FIFRA SCIENTIFIC ADVISORY PANEL (SAP)

OPEN MEETING

USE OF PHARMACOKINETIC DATA TO REFINE CARBARYL RISK ESTIMATES FROM ORAL AND DERMAL EXPOSURE

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C O N T E N T S

DR. HEERINGA: Good morning and welcome to the December 2nd, meeting of the FIFRA Scientific Advisory Panel on the topic of the use of pharmacokinetic data to refine carbaryl risk estimates from oral and dermal exposure.

I'm Steve Heeringa of the University of Michigan. I will be the Chair for today's session, FIFRA SAP. We have assembled an expert panel to address the scientific topic of today's meeting and to answer the questions that have been directed to the panel by the EPA.

I would like to have the members, at this point in the process, of the panel introduce themselves, and I'll begin on my right with Dr. Ruby Reed.

DR. REED: I'm Nu-may Ruby Reed from the California Environmental Protection Agency. I'm a risk assessor. I do pesticide risk assessment and address risk assessment issues for our group. I also teach a class at UC Davis on risk assessment.

DR. FISCHER: I'm Larry Fischer from Michigan State University, environmental toxicology and biochemical toxicology.

DR. PESSAH: I'm Isaac Pessah from the University of California, Davis. I'm a molecular and cellular toxicologist interested in cell signaling.

DR. STINCHCOMB: I'm Audra Stinchcomb, University of Kentucky, College of Pharmacy. My research interests are transdermal drug delivery and internasal drug delivery.

DR. BUNGE: I'm Annette Bunge from the Colorado School of Mines Department of Engineering. My research interest is in dermal mechanisms and penetration measurements.

DR. WHEELER: I'm Mike Wheeler from the University of North Carolina at Chapel Hill, Departments of Nutrition and Pharmacology. I study immunotoxicology and liver toxicology.

DR. HARRY: I'm Jean Harry from the National Institute of Environmental Health Sciences. I'm head of the neurotoxicology group there.

DR. RIVIERE: I'm Dr. Riviere, North Carolina State University, pharmacokinetics, dermal absorption and chemical mixtures.

DR. BRIMIJOIN: Steve Brimijoin, I'm a professor of molecular pharmacology at the Mayo Clinic. I'm interested in the biology, pharmacology of cholinesterases and also pharmacokinetics.

DR. LU: I'm Alex Lu from Emory University, Rollins School of Public Health. I'm interested in exposure assessment and biomarket development for chemical exposures, specifically for pesticides.

DR. KEHRER: Jim Kehrer, University of Texas at Austin. I work on molecular toxicology and apitosis signaling pathways and free radicals.

DR. HATTIS: Dale Hattis, Clark University. I do risk assessment modeling, often on issues of toxic mechanisms, interindividual variability and uncertainty.

DR. EDLER: Lutz Edler, German Cancer Research Center in Heidelberg. I'm doing kinetics, modeling and data analysis.

DR. HANDWERGER: I'm Stuart Handwerger, University of Cincinnati. I'm a pediatric endocrinologist, clinically. My research is in molecular and developmental endocrinology. I'm primarily interested

in molecular mechanisms of fetal growth.

DR. PORTIER: I'm Ken Portier, Statistician, College of Agriculture, University of Florida. My interests are in statistical issues in risk assessment.

DR. CHAMBERS: I'm Jan Chambers with the College of Veterinary Medicine at Mississippi State University. I'm a pesticide toxicologist emphasizing neurotoxicology and metabolism.

DR. ISOM: I'm Gary Isom, a neurotoxicologist from Perdue University. Research interests are in mechanisms of neural degeneration.

DR. HEERINGA: Thank you very much. Peter MacDonald?

DR. MACDONALD: I'm sorry to have been late. I'm Peter Macdonald, McMaster University in Canada, professor of mathematics and statistics with a general expertise in applied statistics.

DR. HEERINGA: Thank you, again, to members of the panel for agreeing to attend today's session.

As you can see, we have a broad variety of scientific and statistical expertise to address the

questions that have been posed to us.

Before we begin today's session, I would like to turn to the designated federal official for today's meeting of the FIFRA SAP, Mr. Joe Bailey, for any additional administrative comments he may have.

MR. BAILEY: Thank you, Dr. Heeringa. As Dr. Heeringa said, my name is Joe Bailey. I'm the designated federal official for this FIFRA SAP meeting.

I also would like to personally thank the panel for giving their time and efforts towards this particular meeting and topic. And I would like to thank the public for attending this meeting as well.

The FIFRA SAP is a federal advisory committee that provides independent scientific peer review and advice to the agency on pesticide issues as they relate to proposed regulatory actions that may affect human health in the environment.

The SAP only provides advice and recommendations to the agency. Ultimate decisions and implementation actions remain, ultimately, with the EPA.

As the DFO for this meeting, I serve as the

liaison between the panel and the agency and am responsible for ensuring that all provisions of the Federal Advisory Committee Act are met.

One of the critical responsibilities is to work with appropriate agency officials to ensure that all appropriate ethic regulations are satisfied. To that end, members of the panel are briefed with provisions of the federal conflict of interest laws.

And each participant has filled in a standard government financial disclosure report that we have reviewed. I, along with the deputy ethics officer for the Office of Prevention, Pesticides and Toxic Substances and in consultation with the Office of General Counsel, have reviewed these forms to ensure that all ethic requirements have been met.

A couple of elements of the FACA requirements I wanted to mention is that this is a public meeting, and we do provide an opportunity for public comments.

For this particular meeting we do already have one person who has identified themselves to make comments. If there is anyone else here who would like to make

comments, either let myself or one of the other members of the SAP staff know.

And if you haven't made prior arrangements, we would like to ask that you keep your comments today to five minutes.

Also, as part of the FACA requirements we have established a public docket. And this public docket contains all of the background materials, questions posed by the agency to the panel and other documents that are relevant to this particular meeting.

Slides that are being presented at today's meeting will be available in that public docket shortly. We will try to get them there as soon as we can. So within a day or so, any slides that are presented today should be in the docket.

The agenda that is provided today provides contacts for both the docket and EPA's website which also contains the background documents.

At the conclusion of today's meeting, we will prepare a report that serves as the meeting minutes. It will provide responses to all the questions posed by the

agency. And the responses will consider the presentations that are made today, the background materials, and any public comments that are made.

And in general, we anticipate that a final report will be available to the public within a six to eight-week time frame after the conclusion of this meeting.

That concludes my remarks this morning. Again, I would like to thank the panel for being here today. I will turn back to Dr. Heeringa.

DR. HEERINGA: Thank you, very much, Joe.

Just a few procedural issues. For those of you who will be speaking today, including the panel members, as mentioned to the panel members earlier, we are recording this for the record and it will also be transcribed.

It is very important that when you come to the mic that you be identified as the speaker. In some cases I will actually call on you, and that's sufficient.

But if we get into a conversational mode here and you do come up to the mic -- the toughest thing I

think for the scientists around the table, and others, is to identify themselves before they begin talking. But it is very important for these proceedings, so if I could urge you to do that.

Be sure to speak clearly into the microphone, too, so members of the audience can hear it and also that it is picked up effectively by the recording as well.

At this point, I guess I would like to open today's agenda by welcoming Mr. Joe Merenda, who is the Director of the Office of Science Coordination Policy for the EPA, for some initial remarks.

MR. MERENDA: Good morning. Thank you, Steve. I would like to take this opportunity to welcome the panel to this session. This is the third of four days, the second of three meetings for the FIFRA Scientific Advisory Panel this week.

I certainly want to particularly thank those of you whom I also welcomed two mornings ago at the start of another session for your continued commitment and perseverance.

This is a very strenuous schedule that we have

set for you this week. We're very pleased at the number of panel members, particularly the five permanent panel members sitting here today who were able to commit to serving on consecutive sessions, which is quite a major drain on your time, as well as, I'm sure, your stamina.

The FIFRA Scientific Advisory Panel is the procedure that the Office of Prevention, Pesticides and Toxic Substances in EPA uses to get peer comment and peer review of major scientific products related principally to the EPA pesticide programs, occasionally to other science issue that are related to our pesticide programs.

Within EPA, the availability of this sort of external comment and advice is very important to us. The agency is strongly committed to implementing a process of transparent, rigorous, independent, external peer review of its major scientific products, and this type of panel meeting is one of the preeminent forms in which we pursue that goal.

The work of the panel is, as I mentioned before, challenging. We tend to throw you a lot of complicated questions and often huge amounts of data with a relatively

short period of time to work on them. And we know that you have to devote a lot of preparatory time to actually get ready to give advice in the public session.

So let me thank you for that work that you have already given and for the work to come, which, of course, includes the public session today and then the report writing to follow.

The process, as Joe Bailey pointed out, is a public meeting. And we also welcome the public participation in this process. But the principal reason that we are getting together here is to get the scientific advice of you as a number of independent experts in relevant fields.

And so, again, thank you for your service and welcome to this panel. I apologize that I won't be able to spend too much time with you today. I have a series of meetings back at the office.

I'm still trying to find out when the first one starts. It was supposed to be 10, but I was told I might have to get back even earlier than that. If I dash out, it is not anything anybody said; it is just my calendar

closing in on me.

Thank you very much.

DR. HEERINGA: Thank you very much, Joe.

Also this morning we have from the Health Effects Division of the Office of Pesticide Programs, Dr. Randy Perfetti. Randy, good morning.

DR. PERFETTI: Good morning, Dr. Heeringa, and good morning to the panel. I would like to simply echo Joe's welcome to the panel and also my great thanks for taking your valuable time to be with us here today.

Again, I also was going to say, and I'll say it anyhow, those of you who will be here for four days, I know it is a very tiring and difficult time. Those four days are a difficult time for you.

Today -- I alluded to this on Monday. I would just like to reiterate it now. Today we're going to look at a novel use of pharmacokinetic information to estimate exposures resulting from lawn treatments of pesticides, especially exposure to toddlers.

With that, I would like to say I'm looking forward to a very interesting and informative session

today.

That concludes my remarks. Dr. Heeringa.

DR. HEERINGA: Thank you very much.

At this point I think we're ready to begin the formal scientific component of today's session, and that is going to be a presentation by Dr. Kit Farwell of the EPA.

DR. FARWELL: I would like to say good morning to the panel also, and thank you for being here to hear this presentation. And as Randy mentioned, Bayer CropScience has a proposal to use pharmacokinetic studies in rats to refine risk estimates from oral and dermal exposure to carbaryl.

This is a novel approach which we haven't used before in evaluating pesticide exposure. We're asking your help in evaluating the strength and weaknesses of this approach.

This is what we'll be talking about today. We'll talk about the Bayer mixed-dose study in which rats receive oral and dermal exposure at the same time to mimic estimated children's exposure on lawns.

And we'll talk about how peak brain concentrations were calculated after divided doses. And we'll mention some exposure assessments which have already been conducted by EPA. And we'll talk about how to extrapolate from the mixed-dose study to the biomonitoring study.

Now, as you know, carbaryl is an N-methylcarbamate insecticide which inhibits acetylcholinesterase through carbamylation of the enzyme site and accumulation of acetylcholine causes cholinergic toxicity with rapid recovery of acetylcholinesterase inhibition compared to OPs.

Carbaryl has many ag and residential uses, including uses on lawns, gardens and ornamental plants. And an interim re-registration eligibility decision was issued last summer. It is found on that website.

There is concern for oral and dermal exposure to young children playing on carbaryl treated turf. And the endpoint for oral exposure is decreased cholinesterase activity and cholinergic signs in rats with no observed adverse effect level of one and a lowest observed adverse

effect level at 10 milligrams per kilogram per day.

The endpoint for dermal exposure is decreased brain and red cell cholinesterase activity in a rat dermal study with a NOAEL of 20 and LOAEL of 50 milligrams per kilogram per day.

Now, what we're talking about was presented in Appendix 1, the Bayer proposal, application of carbaryl PK data in estimating potential post-application health risks with broadcast lawn care products.

And in this proposal, PK studies in rats were used to determine peak internal dose in brain for calculating margin-of-exposure. And PK data for the brain was used because the brain is a direct target for cholinesterase inhibition.

And in this proposal, PK data was used to -- also used to estimate peak brain concentrations resulting from 40 divided oral doses instead of two doses which were used in the study. And there was some discussion about applying the PK data to biomonitoring results.

Now, this shows how EPA calculates the margin-of-exposure to assess exposure and risk. The no observed

adverse effect level in rats would be divided by the estimated dose of children playing on turf.

And in this proposal, an MOE is calculated by dividing the peak brain concentration in rats, which were dosed at the NOAEL dose, divided by the peak brain concentration in rats dosed similarly to children's exposure.

So with the EPA method, the rat dose is compared to the children's dose. And in this proposed method, rat concentrations in the target tissue are compared to concentrations in the target tissue in other rats. And the EPA method assesses administered dose. And the proposed method assesses the internal dose in the target tissue.

Just to let you know what is going on, there is some PBPK modeling efforts underway. EPA's Office of Research and Development is conducting ongoing modeling with carbaryl.

Bayer has also sponsored some PBPK modeling of carbaryl by CIIT, which is ongoing. But these are ongoing and we don't know what the results are or will be.

Now, just some background on carbaryl. Carbaryl is rapidly and nearly completely absorbed by the oral route in rats. Dermal absorption is prolonged and incomplete compared to oral absorption. There is little overlap of the peak concentrations.

Metabolites are excreted in bile and there is extensive enterohepatic recirculation. And urine is the major route of excretion for metabolites and 1-Naphthol is the major metabolite.

And just to show you about the rapid and complete oral absorption, in the first bullet is the Bayer Metabolism Study in which peak radioactivity in tissues was reached 15 minutes after an oral dose.

And in the second study, both an intravenous group and an oral group, both had about 90 percent excretion of dose excreted in urine and about nine percent excreted in feces. So just more evidence of the complete absorption.

And we're going to look at some figures from the Bayer Metabolism Study, which is Appendix 2.

And in that study rats received either an oral

dose or an intravenous dose of about 1 or about 9 milligrams per kilogram or they received a dermal dose for 10 hours at higher doses.

And I'm just going to show you the results from the lower doses because we don't have room or time to cover everything. And the lower doses are more relevant.

So this compares an oral dose of 1 milligram per kilogram to an IV dose of 0.80 and this is total radioactivity on the left. And the first sampling period in the oral dose was at 15 minutes, on the top.

The first sampling period, on the bottom, for the IV was at five minutes. And the tissue levels are really very comparable between the two, especially when you look at comparable time intervals.

It is hard to see the brain, which is at the very bottom, but we'll look at that later.

And I know the panel knows more about this than I do, but I just want to explain some things so that the audience stays with us.

This shows radioactivity in brain after an oral dose of 1 milligram per kilogram. You can see the rapid

decline in the first hour or so. And after that, the decline is slower.

And the first phase is called the alpha phase of kinetics in which absorption and redistribution in tissues predominate and later on excretion of the metabolites from the body are predominating.

And these are results from a dermal absorption study which the registrant did a few years ago. And they show that dermal absorption is a slow and ongoing process. And at two hours exposure there was about five percent absorption. And after about 10 hours there was about 13 percent total absorption and about 25 percent after 24 hours.

And in the recent Bayer Metabolism Study, after dermal absorption -- after dermal exposure, peak radioactivity wasn't reached until four hours and this shows results.

This time we're comparing the oral dose, again, this time to the dermal exposure on the bottom. And at the top, the oral dose is 1 milligram per kilogram. And at the bottom the dermal dose is seventeen milligrams per

kilogram.

And you can see that the peak radioactivity for the top, that's plasma, is about one-tenth of the peak radioactivity after the oral dose. And you can also see the peak is reached at the first sampling period after oral exposure at 15 minutes up here.

And over here, after dermal exposure the peak isn't reached until four hours. And you can also see this little bump which happened after dermal exposure of about 15 or 30 minutes which is probably due to acetone, which was used when the dermal application was made.

And it looks like there is really a big tail right here for the dermal exposure but -- compared to the oral. But I think that's just because the scale there is blown up.

Now we're comparing radioactivity in the brain after oral exposure to dermal exposure. And the oral dose is 1 and the dermal dose is 17. That's the results from the last slide. And if I was just going to show one slide here today, I could just show this slide and really we would be done a lot earlier.

But you can see the peak in brain is reached at 15 minutes. It is a lot higher than the peak reached after dermal exposure at four hours.

And you can also see that by the time you reach the dermal peak, by that time the oral peak is declined to a comparable level. And you can also see that after about 12 hours it looks like the two tails are coinciding there.

And just a couple of more -- a little more information on carbaryl.

Recovery of cholinesterase inhibition is rapid, a half-life of about 1.7 hours in rats in one study and a half-life of about 2.6 hours in a study in humans that was reported in the literature.

I don't know if you noticed in your handout it said three hours for rats, but some later calculations showed it to be 1.7. But they are roughly comparable and short lived.

And carbaryl has a short half-life in plasma. Plasma half-life in rats was a little over one hour in one study in the literature and plasma half-life in humans was a little less than an hour in one study reported in the

literature, so short-half life, roughly comparable.

Urine is the major route of excretion, as I mentioned. Most of the radioactivity is excreted in urine in rats. And 1-Naphthol is a major urinary metabolite accounting for about 40 percent of the original dose in rats and humans, depending on how far out you measure the urine.

These are just some metabolites identified in that recent Bayer Metabolism Study. Carbaryl, per se, was seen in brain, fat, liver. It was also seen in plasma after IV dosing, but not after dermal or oral dosing, which is kind of surprising because you know it has to be there; it inhibits red cell cholinesterase. But it wasn't seen.

Another metabolite, major metabolite, was N-hydroxymethyl which was seen in brain. And 1-Naphthol was seen everywhere. And the sulfate conjugate of 1-Naphthol was also seen in plasma.

Now Appendix 3 has the mixed-dose study which is what this proposal is based upon.

This study was designed to mimic children's

simultaneous oral and dermal exposure to carbaryl-treated lawns. The estimated exposure to children on carbaryl-treated turf is due to physical contact on lawns for two hours and mouthing behavior of 20 times per hour for two hours, according to our SOPs for residential assessment.

Now in this mixed-dose study, rats received a dermal dose for two hours of 0.8 milligrams per kilogram and simultaneous oral exposure. They received two oral doses of 0.08 milligrams per kilogram spaced an hour apart.

And these are the results from that study. Plasma is up at the top and brain is at the bottom. And this is total radioactivity. And you can see the rapid decline from 15 minutes. And later on you see a little bump at one hour, which is probably the dermal exposure.

So that was one hour after the second oral dose which would make it three hours after dermal application was started.

And this shows radioactivity in brain after that mixed-dose study. And again, you see the rapid initial decline. And it slows and goes up around three hours.

Now, as I said, children's mouthing behavior is 20 times per hour for two hours according to our SOPs for residential exposure. And in the Bayer mixed-dose study, two oral doses rather than 40 divided doses were used.

And Bayer did not give the rats 40 oral doses in two hour time periods because they said this was impractical and inhumane.

Now, the two oral boluses in the mixed-dose rat study resulted in higher peak brain concentrations than would be expected from 40 divided doses.

Bayer estimated the peak brain concentration that would result from 40 divided doses. Now, to calculate the peak brain concentration from divided doses, you need to know what each individual divided dose is, what the brain concentration resulting from that single divided dose is, and the half-life in brain.

So first, to calculate the divided dose is pretty easy. If you divide the expected children's oral exposure by 40, and get this number, .00375, which is the single dose for each of the 40 doses.

Now, next, you want to know the brain

concentration resulting from that single divided dose.

And the resulting brain concentration from that divided dose was extrapolated to be this small number, which is .000091 parts per million. And this concentration was extrapolated from the three higher doses in the Bayer studies because at that low level it would be below the level of detection.

And next you need to know the half-life in brain. And the half-life of brain was estimated from the alpha phase of kinetics because it was the time period of interest for children on treated lawns.

The carbaryl half-life in brain from the 15 minute to 30 minute period, which was the first two sampling periods, was 15 minutes.

And the half-life for radiolabel in the brain in that same time period was 19 minutes. For the calculations here they were similar and the 19 minute period was used.

This shows how the half-life was calculated. There is nothing fancy here. Over on the right is carbaryl parts per million, which declined from 45 to 23

in the first sampling time period.

And you don't need an expensive pharmacokinetic program to see that there is 50 percent depletion in 15 minutes. So, that was easy. And here the depletion was a little less. That gave a half-life of 19 minutes.

And if you do the same exercise going down the chart, you find longer half-lives to one hour to three hours. I didn't calculate those. But you can see from those numbers and from the earlier figures that, as you would expect, the half-life would be longer with increased time.

Now that we have that information, we can calculate the peak brain concentration resulting from 40 divided oral doses.

So here is an equation which I put up there because pharmacokineticists like equations, but we don't need to use that equation. We can just use a spreadsheet.

Every three minutes we'll add that small concentration to the brain concentration. And every minute subtract .025 of total carbaryl in brain, which that number came from the half-life of carbaryl or

radiolabel. And the peak brain concentration resulting from the 40 oral exposure at that dose, every three minutes, and using that half-life of 20 minutes was estimated to be .0011 parts per million. And the calculations were shown on the spreadsheet which you received as Appendix 4.

Here is a printout from the spreadsheet, which shows a plateau at .0011, I think it was, parts per million. And you can see how the spreadsheet was making the calculations. Every three minutes there would be another oral dose. And every minute there was a small subtraction until you reached the plateau area, which was just calculated for the two-hour period because that was the time period of interest.

Now, this should be Jeff Dawson giving this presentation, but he wanted me to do this part, just a little bit about the exposure assessments which the agency has done.

Now, a deterministic assessment based on our standard operating procedures for residential exposure was conducted. And a probabilistic model with CARES, which

calculates distribution of exposure, was conducted. And a biomonitoring study, which monitored urine from residents were carbaryl was used, was also conducted.

Now, these three agency exposure assessments gave similar results for evaluating total exposure but did not consider peak exposure in the target tissue.

Now, this graph is an output from a CARES probabilistic exposure model that is superimposed with results from the two other exposure assessments for kids playing on carbaryl-treated lawns.

The Y axis shows exposure in milligrams per kilogram per day and the X axis shows percentile of population. The line represents the CARES output. And the two dots in the middle show two different ways of interpreting the central tendency biomonitoring results.

And the dots in the upper right represent two exposure assessments, one following EPA's SOPs and the other showing upper percentile exposure from the biomonitoring study. Results from all three exposure assessments show excellent agreement between these three methods.

Since the exposure assessments considered total cumulative exposure and did not evaluate peak exposure in the target tissue, results from the rat PK study were extrapolated to the biomonitoring study by comparing MOEs.

And in this biomonitoring study, which we have been talking about, 24 hour urine samples were collected from residents in homes who applied carbaryl to lawns.

1-Naphthol was used to estimate carbaryl exposure, and a factor used to convert that 1-Naphthol to absorb carbaryl had been calculated from the rat and human PK data. And in to the biomonitoring study, urinary excretion of 1-Naphthol continued for 96 hours.

Now, we're back to the MOE calculation. And as we looked at earlier, in a traditional MOE calculation, which EPA conducts, the NOAEL, no observed adverse effect level from the rat study is divided by expected toddler exposure, which in this case 1 milligram per kilogram per day divided by .25 gives an MOE of four.

And I can see that there is an error right here in that number. Just ignore that number four on the right. And the peak brain concentration in rats using

this proposed method was, when they were dosed at the oral NOAEL, was .077. When it is divided by the estimated peak brain concentration from repeated oral doses, you have an MOE of 70.

Now, the biomonitoring study evaluated cumulative dose and did not consider divided doses. So an adjustment factor was proposed to extrapolate results from the rat PK study to a biomonitoring study. And this is one way to do it which was in the Bayer proposal.

Because MOE calculated using peak brain concentration was about 20 times the traditional MOE or actually 17.5, results in the biomonitoring study were multiplied times 20, and this is what was presented in the package.

I talked to the Bayer representatives this morning. They showed me some other calculations for doing it some other ways which weren't included in that package. And I'm not going to discuss it, but they are still working on that. And they are here to discuss these issues later on if you have questions.

So just to summarize what we did, we went

through several steps to calculate peak brain concentrations from divided doses. And that's just a repeat of the earlier slide which is here as a reminder.

And the peak brain concentration may be a more accurate indicator of risk than total absorbed dose because of carbaryl's pharmacokinetic and pharmacodynamic characteristics, which are rapid oral absorption and prolonged dermal absorption along with rapid metabolism and brief inhibition of acetylcholinesterase.

Now, traditional risk assessments assume no recovery during the course of a day. And a traditional approach may overestimate combined oral and dermal exposure due to the pharmacokinetic and dynamic characteristics of carbaryl.

And at issue in this SAP meeting is whether peak exposure in target tissue is appropriate to assess carbaryl exposure and if these results can modify results from traditional exposure assessments.

That's the end of my presentation. I'm ready to take questions as appropriate.

DR. HEERINGA: Thank you very much, Dr. Farwell,

and you made reference to Jeffrey Dawson, also from the Health Effects Division, who will be here today too.

Before we open to questions, just a couple of points for the record, I think that the background document you mentioned with regard to half-life of cholinesterase inhibition, both the figures are mentioned in there, the original Bayer proposal and then the revised value cited by Brooks and Broxup, as well. For the panel members that's in your background materials, both numbers were there.

Dr. Farwell, you mentioned additional calculations by Bayer. Our comments and review at this point will be based, obviously, on what we have had a chance to look at. If you feel they are relevant, bring them forward at some point. You might want to offer some clarification.

DR. FARWELL: I will say there are a lot of different approaches. I hope we hear some different approaches or different opinions from you all. I'm not planning on presenting anything extra.

DR. HEERINGA: Very good. For the panel's sake

then we'll obviously review and respond on the basis of the materials we have seen to this point.

At this point I would like to open it to questions for Dr. Farwell on his presentation, general questions from members of the panel.

DR. HATTIS: I have a couple of questions. First, which half-life is being -- which half-life for the cholinesterase inhibition -- which cholinesterase is being referred to in the 1.7 or 3 hour half-life for the rats? Was that --

DR. FARWELL: I think that's plasma cholinesterase.

DR. HATTIS: But do we know then about acetylcholinesterase, that reversal rate?

DR. FARWELL: I would have to look that up. Even with all the rich data on carbaryl, it's a -- probably be something I might have to calculate from different studies. So I don't have the exact, more exact numbers.

DR. HATTIS: I guess -- were brain cholinesterase measurements included in these

pharmacokinetic studies that were --

DR. FARWELL: In the first metabolism study, it had two doses by each of the oral and dermal and in IV routes. And then those studies were selected to be based on the lower dose was, approximately, a NOAEL dose, and the higher dose would be a lower dose at which cholinesterase inhibition would be seen. And they did do cholinesterase testing at the higher dose.

DR. HATTIS: Over time? At different times periods after exposure?

DR. FARWELL: Right. I just presently received that data. I haven't analyzed it.

DR. HATTIS: I guess, fundamentally, the question I have is why do we care about the concentrations of carbaryl itself in the brain rather than the persistence of its cholinesterase inhibition?

DR. FARWELL: Well, at the higher dose, you can measure the cholinesterase inhibition. But at the NOAEL dose, there probably would be either no inhibition or minimal inhibition. And at the lower dose, there should certainly be no inhibition.

DR. HATTIS: No measurable inhibition.

DR. FARWELL: Right.

DR. HATTIS: You certainly would agree that there would be inhibition --

DR. FARWELL: Right.

DR. HATTIS: -- depending upon the biomolecular reaction. But the reversal, the mechanism of reversal of the cholinesterase inhibition, as I understand it, is a simple chemical hydrolysis. Right?

That is not catalyzed by anything. So there is no reason to expect that there is a difference in the regeneration rate of the acetylcholinesterase which you care about at higher low doses.

DR. FARWELL: Well, I would think at very high doses there -- and I know there are some experts here who might jump in, but in some studies that I have seen at much higher doses it seems that inhibition is really much more prolonged and I don't know if that's due to -- must be due to longer accumulation of the chemical in the brain. But at higher doses, much higher doses it seems like there is prolonged inhibition.

DR. HATTIS: Prolonged detected inhibition, --

DR. FARWELL: Right.

DR. HATTIS: -- because you start out with high -- more inhibition.

DR. FARWELL: Right.

DR. HATTIS: That's what I have.

I guess there is one other question. What is the mechanistic -- is there a mechanistic justification for that log log interpolation or is it just for convenience?

DR. FARWELL: I'm sorry, which interpolation?

DR. HATTIS: There was a log log interpolation to get the brain carbaryl levels at the lower dose.

DR. FARWELL: Oh, okay, the interpolation -- I would have to refer to the handout.

DR. HATTIS: The handout has no discussion of a mechanistic justification for that, that model form.

DR. FARWELL: That might be a question I might have to refer to the Bayer group.

DR. HATTIS: Thank you.

DR. HEERINGA: Dr. Brimijoin.

DR. BRIMIJOIN: Let me just -- I have two things. I want to follow up with what Dr. Hattis said. I think it actually is somewhat critical that your model take account of the half-life of the inhibition per se.

We don't actually know -- I don't actually know whether it is longer or shorter with acetylcholinesterase. Its mechanism of recovery is hydrolysis by the affected enzyme. It is not a chemical reaction, it is an enzymatic reaction by the targeted enzyme.

But let's just assume that it is -- I think there are a number of perverse aspects in what we have been hearing. Let's assume that it is about the same. It is hard for me to understand why that isn't -- why that isn't accounted for in the model. I guess we'll get back to that in the comments.

But my number one question for you is why are we looking at brain as the target tissue? What is the basis of selection for that? You are probably going to tell me there are seventeen previous SAPs that decided that this was the appropriate target. But, again, it seems perverse.

We look at that it's -- the actual exposure levels in the brain are tenfold lower than in the other sampled compartments. And, yes, we should be worried about brain. I think about brain all the time. It is my area of research.

But wouldn't we be concerned about let's say gastrointestinal upset in children who are exposed? We're talking about oral exposure. Wouldn't diarrhea be considered an adverse effect?

Why are we not concerned with -- why are we not using the most sensitive compartment, which would be plasma or preferably a peripheral target tissue rather than a protected and remote compartment such as brain?

What is the justification for choosing brain as the target tissue to model here?

DR. FARWELL: We had some discussions along those lines. I don't know of any previous SAP meeting, but the brain would be one direct target.

We discussed using blood or red cells, which red cell acetylcholinesterase can be considered to be a surrogate for the peripheral nervous system. But in that

case would be using pharmacokinetics to model a surrogate which seems like it removes us one step further.

DR. BRIMIJOIN: Maybe I will expand on this when we get to our discussion, but thank you for that clarification.

DR. FARWELL: As far as using other compartments which had higher concentrations, the concentrations were higher so they might be easier to measure more accurate. But then since we're comparing concentration at the two doses, then ratio should be similar.

DR. BRIMIJOIN: I guess it is key. I mean, I guess I'll just come right out and say I think you are modeling the wrong tissue. First of all, you should be trying to model it in some peripheral tissue.

In this case we're thinking about oral exposure and I think the gut is an appropriate tissue to model. But I accept the point that ratio -- the margin-of-exposure might be similar. Then again, they might not because of the peculiar pharmacokinetics of the brain.

DR. HEERINGA: Dr. Lu and then Dr. --

DR. LU: I'm Alex Lu from Emory. I have a

fundamental question for EPA. How relevant at EPA using total radioactive residues in this case?

How relevant that using radio -- total radioactivity residues in this case considering that the registrant can report certain percentages of interest compound, for example, carbaryl, per se in certain specimen samples?

Why not convert all data that present here to just carbaryl and say 1-Naphthol concentration instead of having two sets of data that has total residue -- total radioactive residue and the compound, per se?

It is very confusing sometimes, especially, when you use these two data and convert to each other. There is a lot of misleading information presented. So I would -- I just wonder.

DR. FARWELL: I think it is just easier to measure the radioactivity and at higher concentrations than to account for the amount of carbaryl. But --

DR. LU: My argument here is that if we are only interested in the peak concentration, regardless of the dose that was used and the route of administration,

obviously, the registrant can identify how many percentage of those radioactive belong to what compound, then why don't we just go for that direction instead of having all the conversion data reported.

DR. HEERINGA: Dr. Edler.

DR. EDLER: Two questions, one is the NOAEL, you had at the 1 milligram per kilogram, what were the -- that was a rat study, and what were the endpoints of that NOAEL, everything or just the brain?

DR. FARWELL: In that study, brain cholinesterase and red cell and whole blood cholinesterase were decreased. And also plasma cholinesterase and cholinergic signs were seen.

DR. EDLER: The other thing is more fundamental, actually. I think the whole MOE, margin-of-exposure principle was investigated in some way -- as one example if you have very, very, low concentrations of some substance, and you don't see anything though you want just to get to some decision on that substance.

So you always look for what people will get finally or could be exposed to some extent. That's why

you actually use the administrative dose to calculate the MOE. Now in this time we have, I think, we shift in some way this paradigm.

My question would be are there similar cases being with EPA in the past where you shifted away from the administrative dose, from the MOE principle? Because for me it is much more a principle than just a calculation method.

DR. FARWELL: I believe there have been some efforts in some other parts of EPA, not here in the pesticides program, though.

DR. HEERINGA: Dr. MacDonald.

DR. MACDONALD: One thing I'm missing here. The biomonitoring study, you are looking at the concentration in urine. Where is the data that connects the concentration in urine to the concentration in other parts of the body, other organs, where it may be doing damage?

DR. FARWELL: Well, literature review was conducted looking at rat and human pharmacokinetics that was used to calculate the conversion factor for converting naphthol to carbaryl.

That study would give you a conversion factor, which would account for the total absorbed dose of carbaryl but not for at what time periods it was given or by what route.

DR. HEERINGA: Dr. Portier.

DR. PORTIER: One of the things you didn't cover was the sensitivity analysis that was done on the model. And I had a question on Table 9, where you talked about how the brain level effects go up and down as you change some of the parameters in the exposure, primarily in the exposure component of the model.

In particular, you used a clustering of dosing rather than the uniform dosing. In this model you have done it 40 times in 2 hours every 3 minutes.

The alternative for the sensitivity analysis was clustering four events per hour, four clusters of four events per hour spaced at ten minutes. I'm assuming you have six finger-sucking, hands-in-your-mouth events every ten minutes.

My question was were those six events uniform as well within some period of time? It wasn't clear in the

documentation.

DR. FARWELL: That was from -- that table was from the Bayer proposal. I would have to -- I think I would have to refer you to the Bayer people for that calculation.

MR. DAWSON: Kathleen Martin, can you put that slide up? It is in the file, the Table 9, that Dr. Portier was referring to.

I believe the data that Dr. Portier is referring to is from behavioral videography of children of this age group. So essentially -- that's it right there.

So essentially, that represents those children's behavior. It just so happens that during the time frames when they were videotaped that that's just the empirical data that was collected monitoring their behavior.

As far as exactly what it looks like, I would have to, maybe at a break, try to figure that out in more detail. But that's what that represents.

DR. PORTIER: This is important because in the little graph that you showed that has things kind of

jagging up until it reaches a peak and then kind of levels out and starts to go down again, that's assuming you have a little jump every three minutes on your 40 minute doses.

And once you start clustering, those jumps can jump much faster. I wondered how they did that. Whether it was done with random intervals or whether it was uniform intervals in the sensitivity analysis.

MR. DAWSON: Right. The initial analysis was just assuming uniform distribution. And then this is just, if you will, real life or empirical data for selected children from videotaping.

DR. HEERINGA: Dr. Riviere.

DR. RIVIERE: I'm not sure if this is the right time to comment on this. My biggest concern with this is that you are assuming that the humans getting dose, say, every three minutes by fingering.

But that doesn't directly correlate that there is an input into the system every three minutes. Because everything goes into the stomach and then there is a gastric emptying that essentially pulses, you know, in this case the carbaryl into the intestinal tract.

So showing that accumulation base -- I'm not sure in rats, and I'll mention this on the discussion point on what the actual gastric emptying time repeatedly in rats is, but in humans it is a lot longer than three minutes.

So the actual rate limiting input into that system is not the three minute dosing. It is the release from the stomach, which is going to -- looking at that sensitivity analysis can really change what those potential brain cholinesterase levels are.

And there are a few other points I'm not sure -- I'm sure some other people will bring up what a real half-life is. Just looking at that alpha phase, that is not really the half-life. Because you have to sort of take into account what the terminal elimination phase was to get at what that number is.

So there are just some concerns of, it looks nice looking at what those intervals actually are, but that's not what the interval is when it comes to the absorption.

DR. HEERINGA: Dr. Reed.

DR. REED: I'm curious about -- in the Bayer study have there been any record or observations on cholinergic signs? Some of the doses are fairly high.

DR. FARWELL: The first study, the first metabolism study, had the higher doses which there should be some cholinesterase inhibition. But they didn't report cholinergic signs in that report. I'm not sure that they were really looking very closely for them, though.

DR. REED: But you haven't looked at the cholinesterase data?

DR. FARWELL: No.

DR. REED: My second question is that -- could you go over again what is the intent of using that adjustment factor of 20 in risk assessment?

DR. FARWELL: Well, that was an approach. This was one approach to extrapolating from the rat pharmacokinetics to the biomonitoring.

And with results -- with an MOE from using the divided doses approximately twentyfold greater than using the traditional exposure assessment, which assessed total dose, then results in the biomonitoring were multiplied by

the same factor.

DR. REED: Would it be used only within the exposure scenario that we're talking about in this comparison or is it going to be used on other occasions for -- like you have biomonitoring data from other scenarios. Would you apply that to it?

DR. FARWELL: I think you would have to do some other studies to relate them to other exposure scenarios.

DR. REED: Thank you.

DR. HEERINGA: Dr. Hattis.

DR. HATTIS: On that, following up, if I am -- I haven't completely reconstructed the 20. But if I'm getting it from the analysis, I gather that part of the 20 probably results from that nonlinearity that you have captured in the log log high dose to low dose projection. And part of it comes from the short half-life of the carbaryl in the brain. Is that about right?

DR. FARWELL: Well, I really would have to go through all the steps again to account for everything. Those are some of the highlights. But -- well, amongst other things, one major difference would be the plateau

brain concentration from divided doses.

DR. HEERINGA: Dr. Fischer.

DR. FISCHER: I would like to say that I'm very skeptical about the validity of the pharmacokinetics that were used to calculate the accumulation of the chemical.

First of all, I think looking at total radioactivity, as mentioned before, is simply an ancient and wrong thing to do in this day.

The active component carbaryl, assuming the metabolites are inactive, should be measured and the kinetics done on the active principle, maybe using cholinesterase inhibition perhaps as a marker for that.

But in any case, I just don't understand looking at total radioactivity and taking half-lives and making any decisions from that, simply because you are not looking at the active principle.

And pharmacokinetics are really based on being first order relationships and the elimination of the chemical. But, in fact, it is reported by Bayer that they found that half-life at lower doses of carbaryl was smaller than the half-life at higher doses. And that

tells you right there that perhaps this isn't a first order kinetic situation that's going on.

So in summary, I just am very skeptical to see -- very skeptical about the validity of using the kinetic approach that was used.

DR. HEERINGA: Dr. Stinchcomb.

DR. STINCHCOMB: I'm just wondering, do we have the data for sure that the metabolites have no toxicity?

DR. FARWELL: Let's see. I'm thinking of -- N-hydroxymethyl carbaryl was detected in brain. And that would be active metabolite. And I think the other metabolites were at lower concentrations. They weren't identified in this study.

That's all the answer I have for that.

DR. HEERINGA: Dr. Stinchcomb, you asked about toxicity of these metabolites.

Is that -- not being a chemist, I don't know. It sounded like they could --

DR. STINCHCOMB: Well, if there is no data, then there is no data. If you don't have -- I think I was reading that because the hydrolysis product was more

hydrophilic, that it was assumed it wasn't as important.

But I didn't know that that seemed right, I guess.

DR. FARWELL: Some of the other metabolites, the major metabolite excreted in urine, naphthol, is a non -- it is not an inhibitor of acetylcholinesterase. And some of the active compounds which are conjugated would not be expected to be active as long as they are conjugated.

DR. STINCHCOMB: But what about other toxicities besides inhibition of the cholinesterase?

DR. FARWELL: I would expect that to be -- expect the cholinesterase to be a very sensitive indicator of toxicity. And probably at larger doses some of these compounds would have some other toxicities.

DR. HEERINGA: Dr. Pessah.

DR. PESSAH: I think the primary purpose for this analysis is to predict toxicity to toddlers, as I read this, and I figure toddlers are between 18 months and 3 years of age.

How does this study in 200 gram, 7 week old rats predict toxicity at a much younger developmental stage?

DR. FARWELL: The only comparative cholinesterase study I know is one that was done in rats by Stephanie Padilla (ph), which compared weanling rats to adult rats and found that adult rats were more sensitive to cholinesterase inhibition in several compartments and had motor activity inhibited to a greater degree and for a longer period than the weanlings did.

That's the only real comparative data I have.

DR. HEERINGA: Dr. Bunge.

DR. BUNGE: One of the arguments of the -- is that peak tissue concentrations of the carbaryl from the oral exposures don't overlap with the peak concentrations from the dermal exposure and that the dermal exposure peak concentration is small enough that -- so therefore, in the revised MOE calculations they basically are ignoring the dermal contribution.

One problem though with dermal absorption determinations is that the applied area or the area in which the administered dose is applied matters more than the administered dose.

And in particular, applying the same

administered dose to a larger area changes the percent absorption. It usually, in some cases, can increase it substantially. So the conclusion about this really rests on whether the administered dose is applied on a relevant area and those are never reported in this document. So it is a little bit hard for us to judge.

So for example, you report some dermal absorption measurements from a study that we don't have the data for other than the results in your presentation. I think it was Slide 16.

Do we know what the applied area was?

DR. FARWELL: You want to flip to the back pocket slides, Kathleen? I think it is one of the last slides there.

DR. BUNGE: You were reporting 2 and 10 -- you were reporting the low dose, I believe, 35.6 results. Because the 2 hour was 5.4, 10 hour, 12.7 and 24, 25 percent.

I would just like to point out that we do see the effect I just described, that when you have a tenfold larger dose, which is the right-hand column compared to

the lower dose, that you saw a tenfold increase at the lower dose in the percent absorbed.

Okay. Let me think about these numbers.

While I'm thinking, though, about those, let me ask you about one other one. In NOAEL dermal tox study, do we know what the areas were?

DR. FARWELL: What was the area? How large was the area applied? I will have to look that up.

DR. HEERINGA: While the panel is thinking, I think from my notes there are really two questions, one of them is this area of the dermal application in the NOAEL study. The other is Dr. Hattis' question regarding the mathematics of the interpolation, the log log interpolation.

One other point I want to make sure -- because as we get into the questions, I think it is essential that the responses to the questions -- it is essential that the panel understand these mechanisms and that there be no question about those.

Going back to Dr. Lu's question, your concern there is really with regard to essentially measuring the

radioactivity levels, can we not essentially calibrate those into carbaryl active carbaryl concentrations.

I don't know the answer. I'm not expert enough to know that.

Is it your view that we should be able to do that with appropriate marking?

DR. LU: There are two concerns here. One is, I thought the EPA does not accept the radioactive data anymore. That's one thing that I probably -- maybe that's my mistake. But for some -- I don't know.

Last year or so I read a statement from EPA saying that EPA no longer recognizes radioactive data as tangible, as good data. Mainly because in this case if you look at this metabolite result, the total TRR actually include not only carbaryl concentration but other metabolites as well. If you only analyze TRR results, the following outcome may not be specific to carbaryl.

So the question is that if that's the case, then what is being presented here wouldn't be, you know -- you are totally wrong because they are not specific to

carbaryl.

DR. HEERINGA: Dr. Perfetti.

DR. PERFETTI: By measuring the TRR, as opposed to the carbaryl or any other metabolites that inhibit acetylcholinesterase, we're being very conservative, which is basically one of our MOs, is to -- if you are going to err, err on the conservative side.

DR. HEERINGA: Thank you, Dr. Perfetti. Yes, Dr. Riviere.

DR. RIVIERE: One other question related to the dermal. In addition to the surface area, this was applied on a Band-Aid, I think I remember reading. And then was that Band-Aid left on the entire time?
Because someone indicated that in looking this over, the acetone evaporated to something leaving an aqueous vehicle. But in reality if the thing was dosed with a Band-Aid the whole time, concluded that acetone is not going to evaporate.

If anything, that could modify the whole situation. So, just a point of clarification, was it dosed on a Band-Aid and then a Band-Aid was left on the

animals?

DR. FARWELL: If we require clarification from the registrant or from Bayer or someone else, if they could please come forward. There is a public commentor mic there or they could use one here. Please, identify yourself too. Thank you.

DR. LUNCHICK: Curt Lunchick from Bayer CropScience. In regards to the dermal dosing, the material was applied at 50 percent acetone solution to the bandage. It was allowed to dry for a few minutes and then was applied to the animal's back.

One other point of clarification is, in the metabolism studies we initially looked at total radioactive residue because we knew we would be able to identify that. We, in addition, looked at specific metabolites and the reports contain the information. And the calculations are based actually on carbaryl and not the total radioactive residues.

We were able to identify carbaryl, 1-Naphthol, the 1-Naphthol sulfate and then there were large amounts of conjugated materials that on the chromatographs were to

the left of the naphthol. So most of our work is done on carbaryl and not just the total radioactive residues.

DR. HEERINGA: Thank you very much. Dr. Fischer, please if you could.

DR. FISCHER: I'm confused because the charts said total radioactivity. Are you telling us that all of the values that we're looking at on the charts, the curves and so on, represent unchanged carbaryl?

DR. LUNCHICK: Curt Lunchick, again. The reports that were submitted to the agency contain charts or graphs, both with total radioactive residues and then with carbaryl where we were able to find it, specifically, in the brain. And the tissue levels that the -- ratio of 20 is based on carbaryl, not the total radioactive residues. Plasma, if I remember correctly, and, Mike, correct me, we could not find carbaryl. Carbaryl seemed to be almost instantaneously hydrolyzed within those first 15 minutes.

So while we were finding radioactive residues in the plasma, and you can see the decay curves that Kit was showing, we were unable to quantify any carbaryl in the

plasma as say compared to the brain where clearly it was hanging on much longer.

And that was part of our emphasis for basing the risk assessment on the brain tissue levels.

DR. HEERINGA: Dr. Reed, do you have a question for Dr. Lunchick?

DR. REED: I noticed that with the first study, the three route separately study, in the brain you did identified N-hydroxy carbaryl, but no 1-Naphthol-Sulfate. In the mixture study it is the other way around. You don't have an N-hydroxy in the brain.

Could you expand on the different metabolites that you find from the two studies?

DR. LUNCHICK: I'm going to defer this question to Mike Krolski, who actually did the studies and has a lot of that down more pat than I do.

DR. REED: Thank you.

DR. HEERINGA: Absolutely, thank you.

DR. KROLSKI: Mike Krolski, from Bayer CropScience. If I remember correctly, the N-hydroxymethyl carbaryl was only found in brain from the high dose level.

I believe it was the IV dosing.

DR. REED: Both the oral and IV?

DR. KROLSKI: Both oral and IV. My guess is that if it was there in the low dose level, it was below the limit of quantitation of our instrumentation, which was in the tenth of a part per billion range.

DR. REED: Could I follow up with that?

DR. HEERINGA: Yes, Dr. Reed.

DR. REED: But then you don't find Naphthol-Sulfate in the brain with that study. But then you found the hydroxy carbaryl in the low dose -- I mean the mixture study, but not the other way around. It was just a switch. I was wondering what could it possibly be.

DR. KROLSKI: I would not venture to guess on the mechanism for that.

DR. REED: But it does present a, sort of, appearance of discrepancies.

DR. HEERINGA: Thank you, Dr. Reed. I guess if there is any clarification to be brought on that point before this discussion is over, feel free to let Mr. Dawson or Dr. Farwell know.

Yes, Dr. Brimijoin.

DR. BRIMIJOIN: I'll just see if I can phrase this simply enough. So Dr. Perfetti has told us that the use of total radioactivity in the brain would be conservative.

I guess what you mean is that, if anything, it would overestimate the amount of carbaryl in the brain. So we can be a little comfortable about that.

What I would like to know is if we're using total radioactivity to estimate the half-life of carbaryl in the brain, do we have any data where you are able to sort out the metabolites to tell us whether the actual decay rate of carbaryl is no slower than that of total radioactivity?

So in other words, that the proportion of the radioactivity that represents carbaryl does not increase as the total radioactivity declines.

DR. FARWELL: Kathleen, can you jump back to the slide show, the main slide show, up to the beginning. Just go up a couple of pages. It shows the half-life for the same time period for carbaryl and the radiolabel. It

would be Slide 35. So for that time period at least -- I'm sorry, slide 36.

I just mentioned, in some of my figures I show the decline of total radioactivity in brain. Maybe it would have been better if I showed carbaryl in brain.

I apologize if that led to any confusion.

DR. BUNGE: If I could ask one more clarification question, back to the Band-Aid application technique on the dermal absorption.

As I understood it, the mixture of acetone, water solution was put onto the Band-Aid. And it was allowed to evaporate for I think it was two minutes to let the acetone disappear.

My question is was there liquid still there -- so in other words, was a significant amount of the water still there so that when the Band-Aid was applied it was moist, and did it stay moist during the application time?

DR. KROLSKI: After the two minutes, essentially what was left was an aqueous suspension. It was obvious there was still water on the Band-Aid on the surface. The surface area was one inch by two inches, which was

approximately 10 percent of the rat's surface area, somewhere around that.

And it was -- the animals were shaved the day before application.

DR. REED: Okay. Thanks.

DR. KROLSKI: So it was applied to bare skin.

DR. HEERINGA: Dr. Stinchcomb and then Dr. Wheeler.

DR. STINCHCOMB: Were there any in vitro human skin diffusion studies done?

I'm asking because I work with a lot of different pro drugs. And the carbamates are actually the ones where I don't get good correlation for human. And I use guinea pig skin.

DR. LUNCHICK: This is Curt Lunchick from Bayer CropScience. As part of this effort we didn't do any in vitro work at all.

DR. HEERINGA: Dr. Wheeler.

DR. WHEELER: It seems from the mixed-dosing model that you are interested in modeling incremental doses over a period of time and you chose to do the two

bolus because of practical reasons.

Did you ever consider something like intragastric gavage where stomachs were cannulated, where you could actually deliver that drug compound over the two-hour window? DR. LUNCHICK: This is Curt Lunchick, again, from Bayer CropScience. No, we did not.

This was a first try at trying to address dealing with dose levels well below where the entire tox database would show there is cholinesterase inhibition. And we need to look for alternatives to try to refine the risk assessment.

To be honest with you, in hindsight, from what we have learned, we would make changes. I think it was part of a learning process. And trying to refine some of the areas such as doing an intragastric gavage like that would probably be worth considering the next time we do a study like this.

I think it is going to be a learning process as we continue to look at metabolism studies like this as part of a risk assessment process.

DR. HEERINGA: Dr. Reed.

DR. REED: I'm sorry. Let me, because I thought I was clear, and then I was confused about the bandage application.

So the couple minutes that you lift the bandage up, you think the acetone is gone? But then I thought in the agency's presentation there was a little bump on the dermal time curve. And I thought it was interpreted as effective acetone.

DR. KROLSKI: This is Mike Krolski from Bayer CropScience. In the two minutes, the bulk of the acetone did evaporate.

However, the only explanation we could come up with for the reason there is that small bump early on in the dermal study was the possibility of transport across the skin by a small amount of residual acetone.

DR. HEERINGA: Yes, Dr. Edler.

DR. EDLER: That poses, actually, a question which may come up later in the day on the variability you have in this data overall.

What you presented here or the EPA presented, just the means of everything, there are means of means of

animal and there are means of these four replicates which are very nicely, actually, very nicely written down in the document.

So did you check if this bumping is caused by one animal, for instance, and not by all animals? How is the variability in this bumping?

DR. KROLSKI: Mike Krolski, Bayer CropScience. It is consistent across all animals within a dose group.

DR. HEERINGA: Dr. Riviere.

DR. RIVIERE: One really fast question, that bumping is based on total residues?

DR. KROLSKI: Yes.

DR. HEERINGA: Dr. Bunge.

DR. BUNGE: Back to the Band-Aid, how do you know that the entire administered dose is actually available or has access to the skin surface that it doesn't get held up in the -- there is some sort of fabric or the gauze that's on the backside of the Band-Aid.

DR. KROLSKI: We don't know. We did not do a study to show retention upon the gauze. It is a waterproof backing with two layers of gauze. And this is

similar to what is used for guideline EPA dermal absorption studies.

DR. HEERINGA: Dr. Bunge.

DR. BUNGE: My understanding is that the guideline studies say that it should be un-occluded or occluded covered with a nonocclusive covering.

So, in fact, that was going to be my next question. How was it actually applied when you did the guideline studies?

DR. FARWELL: I can look it up when I have a chance and check on the guideline requirements and what was done in the other studies.

DR. BUNGE: They are simply guidelines. So each registrant can apply them in somewhat modified ways. It may be that you applied it in the same way.

But I'm pretty confident that the guidelines say that the site is to be covered so the animal can't lick or otherwise lose material. But that it's supposed to be nonocclusive.

DR. LUNCHICK: This is Curt Lunchick. I just want to add a little. Our intent was to try in some way

to mimic, obviously, what is going on in the yard when the kids are contacting the grass.

The use of the Band-Aid and whatever occlusion would tend to be a worst case compared to open skin contact. And the intent of our study was also -- we didn't intend to do a mass balance.

Obviously, that could have been done. Part of this was time frame, tight time frame and things like that and, again, part of a learning process to which improvements could be made in future studies.

DR. HEERINGA: Dr. Bunge.

DR. BUNGE: One or two last things. I think it would be a worst case or conservative with the occlusion, provided that we are confident that the administered dose isn't in any way held up in the gauze material. That it is readily accessible. So that's one concern.

The second question I have is in the risk assessment to arrive at this sort of typical dose that might be expected, there is probably an estimated area of exposure on these kids. And we need that to estimate whether or not the administered dose on a per area basis

is sensible or not.

Do we know what that is?

DR. HEERINGA: Mr. Dawson.

MR. DAWSON: Essentially, the model we use is a whole-body approximation of the amount of exposure you get from, let's say, playing on a treated turf for two hours.

We can certainly calculate some kind of dermal loading based on what is known about the surface area of children of that age with total loading estimate.

Normally, the way we do it is not on a per area basis. It is just the amount on the total surface area. And we don't go that extra step. But we could calculate that.

DR. BUNGE: How do you decide what the amount on the whole kid is going to be?

MR. DAWSON: It is a whole body kind of metric based on studies which look at a simulated behavior. And then we just measure the amount in one piece and not try to put on a surface area.

DR. BUNGE: I see. What is the surface area of a kid, a toddler?

MR. DAWSON: I think it is in the six to eight thousand centimeter range. Adults are in the --

DR. BUNGE: I know what adults are.

MR. DAWSON: It's around 20,000. It's around that range.

DR. HEERINGA: Dr. Fischer.

DR. FISCHER: Would you tell me how you extracted brain tissue? I know it was acetone and water. Exactly how many times did you extract it, and did you extract --

DR. KROLSKI: The actual extraction procedure was to blend the tissue three times. I believe it was 9 to 1. Let me look it up real quick.

DR. FISCHER: I think it was 9 to 1.

DR. KROLSKI: Acetonitrile, water. And then after the blending, the mixture was centrifuged and decanted. This was repeated two additional times. The combined supernatants were then concentrated and analyzed by high performance liquid chromatography, and metabolites were isolated and identified by mass spectrometry.

DR. FISCHER: But how much radioactivity was

left unextracted?

DR. KROLSKI: The majority was extracted. Our extract abilities were in the 90 percent range.

DR. HEERINGA: Dr. Reed.

DR. REED: I promise this is going to be my last question.

I know you sort of have attempted to explain why you are not detecting carbaryl in the plasma samples.

But logically, I want to hear it again. Because if you don't have any carbaryl in the plasma or the blood, why would you have carbaryl in the brain? And there is many reasons for that.

But could you take me through again your explanation of why you are not being able to detect carbaryl in the plasma samples?

DR. KROLSKI: Mike Krolski, Bayer CropScience.

What we believe is happening is that carbaryl is present, but it is essentially a one pass system. The carbaryl gets absorbed, makes one pass through the system.

And by the time we take our first measurement from an oral dose, which is 15 minutes, it is -- all the

carbaryl in plasma has been hydrolyzed.

Obviously, there is some short residence time in plasma. Once it gets to a fatty tissue, it can deposit and the fatty tissue essentially sequesters carbaryl intact.

Now, it allows us to also look at possibly some kinetics because now we have carbaryl in the tissue and we can watch how fast it dissipates. But we think what is happening is it is just getting there fast.

If it doesn't make it through the first pass, there is no shot for more carbaryl getting into the brain.

DR. LUNCHICK: Curt Lunchick, I just wanted to add to that that if you look at the IV data at the high dose at five minutes, we did pick up in the plasma carbaryl, which, I think, adds evidence to what Mike is saying of this first pass and the rapid hydrolysis that's going on in that environment.

DR. HEERINGA: Dr. Reed.

DR. REED: So you think it is a timing issue and not a concentration issue or any other --

DR. KROLSKI: I think what we're looking at is

probably just simple first order kinetics of hydrolysis and it is just a timing issue.

DR. REED: Thank you.

DR. HEERINGA: Thank you. At this point, I want to leave a little additional time for questions. But I think we can probably all benefit from a little contemplative time.

I would like to call a break for 15 minutes. And when we return, let's resume with any final questions that the panel members might have.

I thank you Dr. Lunchick and Krolski from Bayer CropSciences for their contributions.

Let's take a short break. I have slightly after 10:15. Let's reconvene at 10:35. We'll return to a few additional questions that may come to mind.

Then following that, if there are no more questions, we'll move on to the period of public comment. Thank you very much.

(Thereupon, a brief recess was taken.)

DR. HEERINGA: Welcome back everybody to today's session of the FIFRA Scientific Advisory Panel on the

topic of the use of pharmacokinetic data to refine carbaryl risk estimates from oral and dermal exposures.

We interrupted our period of comments and clarification questions from the panel for a short break. I would like to return to that.

But first up, we do have a response from Anna Lowit who will discuss the, I think, the interpolation question that Dr. Hattis had raised.

Dr. Lowit.

DR. LOWIT: Actually, I'm not going to address that. Bayer is going to address that question.

DR. HEERINGA: I'm sorry. That's my confusion. You may address it if you want.

DR. LOWIT: I will let Bayer do that.

DR. HEERINGA: Dr. Lunchick.

DR. LUNCHICK: Curt Lunchick, Bayer CropSciences. I want to thank both the agency and the panel for the opportunity to address some of the earlier questions that were asked. And I also wanted to put the purpose of this study into the perspective of why Bayer did it.

The study was done as part of the regulatory risk assessment in which we were dealing with exposures that are much lower than what is seen in the animal toxicology studies, the guideline studies.

The post application toddler exposure is estimated based on SOPs that the agency has developed. For instance, there is a question on the 20 hand insertions an hour, which is a default that comes from videography. It is an upper percentile of the frequency. And, therefore, is done by the agency as a worst case.

Because measuring actual exposures to children, their behavior being so variable when they are outside on the lawn, Bayer had conducted the biomonitoring study to get an idea of where the estimated absorbed dose in actual play circumstances is to the estimate that the agency calculated based on these SOPs of like the 20 hand to mouth insertions an hour.

And what we were able to show, and it is in the agency's risk assessment, is that the agency's SOP estimate is a good upper bound of the maximum exposure.

But then the issue came up because we want to,

unlike normal risk assessments where a lot of the regulatory decisions are made on central tendencies, because we are dealing with children, we do want to look at the upper percentiles of exposure and make sure that we're addressing the potential risk to these children also.

And we needed to look at a different way to do the risk assessment because cholinesterase inhibition we know from the vast tox database that you have with carbaryl that by the time you get down to 1 milligram per kilogram, we're at levels in which cholinesterase inhibition is no longer significant.

And as you get lower than that, of course, it is going to get rapidly into the area where you cannot tell it from the background noise.

And hence, that was the purpose of looking at peak levels, the brain being chosen among others because it is the target organ that is used in the risk assessment. That was the purpose of this exercise.

What is going on also, just to make the panel aware, is the data we have developed being made available,

there is ongoing efforts both within the Office of Research and Development of EPA and by others, to use this information in doing pharmacokinetic modeling.

Some of this I think will be presented tomorrow, and that's going to be an ongoing effort that goes beyond this regulatory effort that we're looking at here today.

And with that, I wanted to turn the mic over to Dr. John Ross, who is going to answer some of the questions that had been raised prior to us coming up in the last session.

DR. HEERINGA: Thank you, Dr. Lunchick.

DR. ROSS: I have taken some notes here and I would like to just respond to some of the questions that I heard that may not have had an adequate answer.

Starting with Dr. Hattis, you asked about the half life of 1.7 hours and which tissue that was. That was human RBC, not plasma.

DR. HATTIS: Good. There was a rat figure. Was that also RBC for the rats?

DR. ROSS: Yes. That's correct.

DR. HATTIS: So the document gives numbers of

2.6 for humans and 1. -- and 3 for rats. So the rat value is now being revised to 1.7. Is that right?

DR. ROSS: That's right.

DR. HATTIS: And that's an RBC red cell cholinesterase.

DR. ROSS: That's correct. We're comparing apple to apples.

You had also asked about why the GI tract as a peripheral tissue wasn't monitored.

DR. HEERINGA: That was Dr. Brimijoin.

DR. ROSS: The issue of peripheral inhibition is an interesting one. We chose the brain because it is a fatty tissue. It is a known target.

And the evidence was that non fatty tissues would be difficult, if not impossible, to detect the parent compound in. For instance, plasma, we failed to detect it.

Dr. Portier had asked about the clustered hand to mouth. And the answer to your question is, yes, those were uniformly timed intervals.

I believe Dr. Riviere had asked about the

emptying rate of the stomach being a primary determinant.

That, based on the data, does not appear to be the case because we see peak levels in blood in 15 minutes or less following an oral dose.

DR. RIVIERA: Following one dose. Right?

DR. ROSS: Following a single dose, yes. Correct. So it suggests being absorbed directly through the wall as opposed to emptying being a limiting factor.

One other issue was the use of total radioactive residues. Those were used for comparison purposes, but for the purpose of calculating any kind of exposure or risk, carbaryl values were used, the parent compound as opposed to total radioactive residues.

DR. HEERINGA: Dr. Edler, did you have a question on one of these?

DR. EDLER: Just a short question to that 15 minutes, actually, because we have the peak at 15 minutes. So the question is what is going on before 15 minutes.

What is the reason it's impossible to do in the experimental system? Because it could be actually higher before the 15 minutes because you are just in the falling

down period of the curve.

DR. ROSS: That's true. Part of that is due to the experimental protocol that was adopted. In hindsight, we might have been able to do that in five, 10 minutes.

DR. HATTIS: In any event, you can model the 15.

DR. ROSS: Right.

DR. HEERINGA: Dr. Reed, do you have a question related to this?

DR. REED: I was wondering as a follow-up question on the oral dosing and we're talking about stomach emptying.

Do you think -- this is done with fasted rats. Do you think food in the stomach is going to make some difference in terms of the absorption and the pattern of it.

DR. LUNCHICK: This is Curt Lunchick. Food in the stomach, when the children last ate -- or the rats. I mean, we're testing in rats trying to model children.

All of those are variables that can impact it. And I think we need to focus or differentiate between what could be done in an academic setting.

Issues that are very interesting and, you know, deserve answers and continued research versus meeting the needs of the agency and the regulatory realm where we're dealing with tremendous amounts of variability and everything from the children's behavior, trying to look at upper bounds to kind of cover some of these other questions that the panel is raising that are very good, and I think you need to keep in mind that we are focusing on what seems to be both from the agency SOPs and the biomonitoring studies where we looked at actual absorbed doses, the maximal exposures that are occurring following a long broadcast application of carbaryl.

DR. REED: Could I follow up with that?

DR. HEERINGA: Sure, Dr. Reed.

DR. REED: Would you say that with fasted animals, which is pretty standard, that compared to, say, having food in the stomach, the peak might not be as high and the time course might be longer?

DR. ROSS: Sure. I think that's the reason that studies are typically done on fasted animals. It is to facilitate absorption.

In the case of food in the stomach, it would probably delay emptying of the stomach and absorption, but there is apparently absorption directly through the stomach wall.

DR. HEERINGA: Dr. Ross, I believe we interrupted you in your sequence of responses, or were you finished at that point?

DR. ROSS: There was only one other. That concerned the nature of the log concentration in the brain versus the log dose response and the extrapolation that was done using that relationship.

That was a purely empirical observation. We see what appears to be a nonlinear relationship. And that's what we went with.

DR. HEERINGA: Thank you very much.

Dr. Lowit, I believe you have something to contribute at this point.

DR. LOWIT: I wasn't going to even stab at that one.

The agency wanted to first sort of bring this back to how we got to the point where we are today.

The agency had done a risk assessment on carbaryl that identified about a four fold margin of exposure for kids playing on the lawn using traditional SOP high-end estimate type exposures.

And as part of our continuing effort to refine our risk assessments, not only on the exposure side, but on the hazard assessment side, Bayer came and offered to do some pharmacokinetic studies.

In our conversations with them on how the experiments would be designed, we had a lot of the same questions that you have, particularly relating to the cholinesterase inhibition.

Regarding that -- if we bring it back to a risk assessment, that we're calculating a margin of exposure, so you have a ratio where you have hopefully a low level of environmental exposure compared against some effect level identified from a study.

And in this case, it is 1 milligram per kilogram identified from a rat study that's assumed to be a level where nothing, no cholinesterase inhibition was observed.

So you are comparing an environmental level

against something that you are not going to be able to detect unless you have so many animals you make your experiment prohibitively large.

We had all these conversations with them and asked the same questions about doing the cholinesterase measurements, not only the brain, but also the blood.

And came to the same conclusion, that in order to make these experiments reasonable in size, that the cholinesterase inhibition, especially at that one milligram per kilogram, that we would not be using that in these calculations in the refinement of the risk assessment.

I can tell you with the background we have been doing for the cumulative assessment, a little bit we'll talk about tomorrow, is that for carbaryl around 3 milligrams per kilogram, which is three times higher than what they are using in their studies, you can only detect about 10 percent.

So at 1, you would be somewhere between 1 and 5 percent brain inhibition at the worst case. To do that experiment would be -- you would need many animals to

detect that. Thus, no cholinesterase in the studies.

DR. REISS: Thank you, Dr. Lowit, for that clarification. I think all of us on the panel recognize that this is a progression into an area that the panel itself has been advocating to be explored for a number of years.

Dr. Chambers.

DR. CHAMBERS: One procedural question. The oral dosing, what was the vehicle and what was the volume of the vehicle used for that.

DR. KROLSKI: For the oral dosing, the vehicle was an aqueous suspension or a solution in a mixture of one-half percent weight to volume carboxy methylcellulose and 1 percent weight to volume tween 80. The dosing volume was typically half a mil.

DR. HEERINGA: Dr. MacDonald.

DR. MACDONALD: When I hear again and again about the difficulty we are having here trying to come up with a reasonable, but still conservative estimate in the presence of a lot of variability, I'm beginning to ask myself are we going to have to move fairly quickly from

this work to a fully stochastic analysis.

DR. HEERINGA: I want to thank everyone for their contributions to this discussion. And before I close this discussion period, just turn to the panel again. Are there any additional questions or points of clarification. Dr. Stinchcomb.

DR. STINCHCOMB: One thing I was thinking about when Dr. Riviere was mentioning the gastric emptying, I think we need to consider maybe the buckle absorption being just as important as oral gastric and small intestine absorption, because we're talking about a toddler.

I'm sure you have all seen a toddler stick their hand in their mouth. It seems like it's there a long time and there is a lot of exposure to the buckle mucosae, and a molecule like this would be very quickly absorbed.

DR. BRIMIJOIN: Just a really quick -- can I ask a repeat on -- I would like to make a note of exactly what the suspension medium was for oral administration. It was a half a mill with half percent carboxy methylcellulose?

DR. KROLSKI: It was an aqueous suspension

containing one-half percent weight to volume carboxy methlycellulose and 1 percent tween 80.

DR. BRIMIJOIN: Tween 80. And the concentration of the drug -- well, you have given us the volume and the dose. That's fine. Thank you.

DR. HEERINGA: Dr. Fischer.

DR. FISCHER: Just very quickly. I'm wondering whether the model of the rat, the adult rat in terms of its relationship to exposure to human toddlers -- this was brought up before. In the documents we got, it is repeatedly said that the rat is a good model for the human for carbaryl.

So now we ask whether the adult rat is a good model for human toddlers.

If there is some data available to justify that statement that it is a good model, I just would like to hear it at this time. If there isn't, I understand why that might not be available.

DR. HEERINGA: Dr. Farwell.

DR. FARWELL: I'm not aware of the comparative pharmacokinetics, but that's why we use our 10 fold

uncertainty factor for the -- one of the reasons for the interspecies, partially accounted for in that as I know. Some of you know.

DR. LUNCHICK: Bayer is unaware of any either. And I concur with what Dr. Farwell just said. That's why we are applying the 10 fold interspecies and 10 fold intraspecies uncertainty factor.

But to add to that, we are working with CIIT and the agency is developing its own model in which human pharmacokinetic data to the extent it is available is being put into models to further refine this as part of ongoing efforts with the cumulative risk assessment to gain a better understanding of what is going on for future risk assessments.

DR. HEERINGA: Thank you very much.

Yes, Dr. Bunge.

DR. BUNGE: If I could ask one further question, not being a toxicologist, rather a dermal absorption specialist, maybe. But one of the issues I see with the dermal absorption's main contribution is in the later times after the oral exposure has occurred.

And what it does is it makes the tail tail off less quickly, which means that it didn't contribute to the peak concentration, but it does make the area under the curve larger, which then comes back to the toxicological question.

Are we definitely certain that the peak concentration is the relevant one in the fact that the amount in the brain is extended a little bit higher than it would have been over a longer period isn't going to matter in this case.

That's crucial to the argument of ignoring the dermal absorption.

DR. HEERINGA: We'll have a chance to comment on that, too, in response to question 2.

Dr. Farwell, if you have anything to --

DR. BUNGE: I'm asking is there some data or evidence you want to --

DR. FARWELL: Just be the basis for considering peak exposure would be the short cholinesterase -- short period of cholinesterase inhibition and rapid elimination of carbaryl from the brain.

As a concept for considering it, perhaps as a series of separate exposures rather than a one total exposure considering the area under the curve.

DR. HEERINGA: Dr. Bunge, it looks like you are thinking.

DR. BUNGE: I accept the argument. I'm just not sure that I reached the conclusion.

Again, I admit that I'm not a toxicologist, but just it isn't evident to me at least that if it is at a higher level for a longer period that it doesn't matter, that all that matters is the peak concentration.

But as was mentioned, this is going to be discussed further.

DR. HEERINGA: We'll return to that with question 2 at this point.

Dr. Wheeler, do you have a question of clarification.

DR. WHEELER: I have kind of a follow up to that. Clearly, I think, toxicologically, peak is the important dose at the active site.

But since the determination of peak is rather

tenuous in toddler exposure models or even in rat models that we have tried to mimic or you tried to mimic, wouldn't area under the curve be a more accurate assessment?

If you take the summation of the compounds detected after a certain amount of time, wouldn't that be kind of -- I don't know how you would do it statistically, but be an approach to get at kind of normalizing where the peak may be?

Since we can't actually ever really determine peak in the real world.

DR. HEERINGA: Kit Farwell, can you just summarize that again.

DR. WHEELER: I don't know how to ask a direct question. But peak is going to be very difficult to assess, I think, because we can mimic it but are we accurately mimicking in the rat model what you would see in a real life situation.

I think that goes back to the original question of the model, this mixed dosing model. Is the two hour bolus dose or the continuous the right model, and that can

be debated too.

But since it is going to be difficult to determine, I think, peak because of the clustering effect and the continual dosing effect versus a bolus effect, can you take the sum, which would be the area under the curve, I guess is the question, and be able to backtrack from there.

I don't know if it is a question or kind of a statement.

DR. FARWELL: It would be an approach to investigate.

DR. HEERINGA: Dr. Handwerger.

DR. HANDWERGER: Talking about imperfections in the model, children don't have intact skin. I have never examined a child who had knees that weren't bruised or didn't have impetigo or didn't have eczema.

And undoubtedly, the absorption of compounds can be very different from that. Of course, the children, part of the body that's going to be most exposed are probably the knees. That's what children fall on.

There may be highly variable absorption from

that. I don't know how you measure that. But none of our models are going to be able to, I think, account for truly what a toddler does.

DR. HEERINGA: Dr. Dawson.

MR. DAWSON: I think to respond to that we should look at -- can we have the slide with the graph of the exposure assessment graph.

We feel very comfortable with the methodology that we have been using that they are predicting. Because, again, this slide here shows three different exposure assessment methodologies.

You can see from the actual biomonitoring, which I believe for children in this age group is 12 to 14 children.

Where the actual one naphthol levels predict on right up next with our standard modeling approaches.

So I think we're comfortable that we're capturing all this kind of nuance issues related to abraded skin or whatever else they may be.

DR. LUNCHICK: I just wanted to add to what Dr. Dawson was saying. These questions that you are raising

are questions we're all dealing with with children's risk assessment.

Because there is so many of these issues from especially behavioral and what they are doing. And that was the purpose of our biomonitoring study that preceded any of this.

Metabolism data was to get a representative range. We did not control their behavior. The only thing that was controlled was we had the lawn application occur and then after that the children -- everybody in the family did whatever they do.

And the contact with the lawn, the activity outside was really the driving factor. It wasn't residue levels or anything. It gets very much at the issues you are raising.

And that's why we're comfortable, is because if you look at these -- the absorbed doses over a four day period, and here we're modeling a single one day period, but the cumulative over the four day period after the lawn application, we're at levels below the dose level that we're trying to model based on the residential SOPs.

DR. HEERINGA: Dr. Kehrer.

DR. KEHRER: I had asked one question this morning. What you just mentioned brought up a question in my mind regarding the lawn exposure.

Was this done according to the recommended application or the way a homeowner really does it?

DR. LUNCHICK: The protocol of the study was to give the homeowner the material, the commercially available material and provide absolutely no instructions whatsoever.

In Missouri, that's actually what occurred. The material was ready to spray, hose end sprayer that you buy at Lowes or Home Depot.

They were given it. They read the instructions. And we actually do see the variability in the actual application rates, the amount of material that was used. That's picked up.

In California where the principal field investigator was Dr. Krieger, Dr. Krieger instructed the participants to apply one container, one quart container of carbaryl, which was not what he was supposed to do.

But added additional insight, actually, because in California where you have fairly small lawns the application rates in that case were beyond what we saw in Missouri and what would be expected.

So we actually got materials in the biomonitoring study that is really an upper end and beyond the realm of reality in the real world case.

DR. HEERINGA: Dr. Lowit.

DR. LOWIT: While this slide is on, it is a good point to come back to the issue of what the appropriate dose metric is, which is essentially the peak versus the area under the curve issue.

Our traditional assessments, the black dots essentially, are doing total exposure. So they are doing -- like the biomonitoring is the total one naphthol over several days. The SOP type is the total over a certain period on the lawn.

And as we move to more refined assessments of looking at internal doses, whether it's the raw dose or the extrapolated dose or the effect, we like to keep in mind that the dose metric -- it may be appropriate to use

a dose metric that's appropriate for that mode of action.

For carbaryl, for example, if cholinesterase is rapidly recovering, you get rapid turnover in the tissues. That may be an appropriate dose metric for its mode of action.

But, of course, we have the same question. That's why we have asked you. But as that is up, I think that sort of brings back to the dose metric issue.

DR. HEERINGA: Thank you. Dr. Lu.

DR. LU: There is a lot of questions that can be answered if we have a complete data set. This report made available by EPA, the title says, pharmacokinetic data and so on and so forth.

But in this report, actually, there is none of the pharmacokinetic data. This only have half life and the peak concentration. And these two data, actually, were calculated by simple mathematical calculation or observations.

You look at the half life that is calculated. It is ridiculously simple. You look at 15 minutes and 30 minutes and the decrease of concentration in half, and

that's 15 minutes of half life.

It is totally not acceptable by any kind of scientific standards. I mean, there are pharmacokinetic models available that you can put in all those time concentration data.

15 minutes, such concentration, 30, an hour, and then have the model calculate. That half life will be more trustworthy than just simple calculation.

The other thing is that we don't know what is going on before the 15 minutes. The registrant just assumes that 15 minutes is the peak concentration. I guess there is a couple panel members that pointed out that peak concentration actually is variable. You don't know whether that's really peak concentration.

In this case, peak concentration is very important because that lead to a lot of calculation at the end. And that would lead to a different conclusion that EPA has MOE for, whereas the MOE is 70 if you base this on a peak concentration.

But you don't have enough data to justify that that peak concentration is true peak concentration. It

truly happened 15 minutes after dosing. What is going on before 15 is unknown. That's very important.

So I guess, again, a lot of questions we'll be able to answer if we have all the information.

DR. HEERINGA: Dr. Lu, again, we'll turn back to this when our responses to the questions.

At this point, are there any other points of clarification that the panel would like to raise?

Make sure that they understand the materials that have been presented and can answer in an informed way the questions that will be posed to them this afternoon.

Not seeing any at this point, I think I would like to bring the presentation period to a close. Just before I do, Dr. Farwell, anything additional that you would like to add at this point?

DR. FARWELL: Nothing.

DR. HEERINGA: I want to thank everybody for their contributions to this session and the representatives from Bayer CropSciences as well as the EPA staff and the Health Effects Division as well.

I'll bring the scientific presentation period to

a close and we'll turn to our period of public comment. We have one scheduled public commentor, Dr. Jennifer Sass of the National Resources Defense Council.

While Dr. Sass is coming forward, if there is anyone else in the audience who would like to contribute a public comment to this session, because you are not scheduled in advance, we would like you to limit it to a short period of 5 to 10 minutes at the most, five minutes ideally.

But if you would like to make a comment and you have not indicated so far, if you would either see someone at the table from the SAP staff, Mr. Larry Dorsey, or come up and just mention it to Mr. Joe Bailey, the designated federal official.

DR. SASS: Thank you for the opportunity to present some quick comments to you and thank you to the members of the Scientific Advisory Panel for coming together on this important issue and spending your time going over these very important issues.

My name is Jennifer Sass. I'm a Ph.D. Scientist in the Health Program with the Natural Resources Defense

Council. It is an environmental nonprofit group here in Washington, D.C. This is where I'm based.

I'm going to present some quick comments on the subject at hand, the use of pharmacokinetic data to refine the carbaryl risk assessment estimates.

It hit me a few days ago, actually, when I was beginning to prepare these, that this is not only the exact day, 20 years ago, that the carbaryl manufacturing plant in Bhopal, India, poisoned a good portion of the town and almost all the workers and citizens living near the plant, but it is actually close to the exact hour in India right now.

This is almost midnight on December 3rd that the Union Carbide Plant began to leak the methyl isocyanate MIC. A lot of people -- it has now been 20 years since that hour and that day until today.

And many groups are discussing what are the lessons learned from Bhopal. In some ways, the lessons learned are pretty easy. The Bhopal plant did everything wrong. It didn't have any of the safety systems that were required.

It didn't have a refrigeration unit that was functioning to cool the MIC, which was a run away reaction. It didn't have scrubbers that were operable to try and neutralize the run away reaction once it started.

It didn't have any flares that would have burned off any of the reactant products that were then emitted into the air. And even the night was still and without a wind.

And so the MIC, which is heavier than air, just stayed in the area, on the town and on the people.

Union Carbide, this ad that is shown here is a 1962 Union Carbide ad for their products. And you see that they are showing the world that they are dumping scientific medicine onto the agriculture fields there to help the plants grow.

That's what the carbaryl was advertised as. Many of the workers in the plant were told that it was medicine for the fields, for the plants.

And when the plant did start to explode, many workers ran towards the plant not knowing how toxic it was to try and help.

The workers on shift that night also stayed trying to make something work when there were no safety systems available.

And other corporate operators, multinational companies, at the time actually had corporate policies of not storing large quantities of phosgene on hand, but actually producing it as it was needed.

But this plant did store millions of pounds, in fact, of phosgene on site. So the phosgene and the MIC, which were both components of carbaryl, caused the poisoning of what is estimated now at over 100,000 people having chronic or long term effects still today.

There is epidemiology coming out of that area showing birth defects and problems in second generation exposed.

Carbaryl is widely used here and abroad. This slide, the information here was taken right off of Bayer's web site a couple days ago when I was preparing this talk. And the web site claims it was updated this month.

That Bayer web site says that Sevin, which is the trade name for carbaryl, controls over 565 pests. They

list a whole bunch of them. It's one of their top products.

It is registered in more than 70 countries around the world. It's a broad usage pesticide. Registration on over 100 crops. It's sold widely in the home and garden markets as well, for commerce, for commercial farming.

Also in that same web site, I looked up whether carbaryl is still made with phosgene and MIC. As far as I could tell from their web site, it is.

These key intermediates and raw materials were listed on their web sites as available from Bayer, both phosgene and methyl isocyanate.

I looked up the TRI, Toxics Release Inventory, to see how much of the carbaryl waste is emitted into the environment through either land, water or air.

And what I found was that it is almost all air. Really, it is all air. When I looked up carbaryl, you can see that it's three or 4,000 pounds -- total is over 4,000 pounds annually.

But that's all into air. It either goes into

fugitive air emissions or on site air emissions. That means it is available for everybody to breathe. Everybody in the neighborhood, everybody who's exposed.

As opposed to, for instance, water which you have to actively intake or underground injection, which is considerably less available.

I also looked up the components, methyl isocyanate and phosgene, to see what their TRI reporting was. And cumulatively, carbaryl and its component products are emitted all into the air either, as I said, on site or by fugitive air emissions at over 22,000 pounds annually.

I looked up the MSDS sheet for carbaryl. There is a lot of acute toxicity effects, which I know that you know, cholinesterase type effects that we would expect with the cholinesterase inhibitor, sweating, nausea, vomiting, blurred vision, abdominal pain. Also noticed fluid in the lung, pulmonary edema.

The interesting thing I think about this is that this is actually a side effect, sorry, a toxic endpoint of phosgene.

Phosgene causes delayed pulmonary edema. It has about a six hour delay. That means that the workers who are exposed in the plants feel fine. They go home and then they die after dinner.

As well, you can see that it has some long term effects, including kidney and nervous system effects. And as well, there is some aspects of cancer hazards, again, long term effects. There is some evidence of mutation in cells.

There is some evidence of reproductive hazards. There is some teratology data in animals. Limited evidence that it may reduce fertility in both males and females, and, again, the chronic effects.

My concern is that not all of these may be mediated by the cholinesterase inhibition in the first 15 minutes in the peaks or in the kind of pharmacokinetic data that is being presented in this model. So it might not be capturing it.

So the question 1 that is posed to you, 1A, is the design of the pharmacokinetic studies and their usefulness. And I'm concerned that the pharmacokinetic

studies, while they may be useful, may not become comprehensive.

They are very unlikely to be comprehensive of all the toxic effects that carbaryl is known to possess. I asked a chemical engineer what he thought about the MSDS sheets.

He was very familiar, of course, with the Bhopal and the carbaryl incident there. And he said that it is possible that there might be some unreacted phosgene associated with the carbaryl.

And that made me wonder. And I wonder if it is a concern to the panel that there might be unreacted phosgene present in the commercially available carbaryl.

But that it might not have -- I don't know what grade carbaryl was used in the tests that are feeding into the pharmacokinetic model.

I don't know if they were purer than commercial grade or if they also contained unreacted phosgene or if there is unreacted phosgene.

But I wonder if it isn't more accurate or more defensible to consider not just the effects of the

carbaryl, per se, as it says in the handouts, but also the effects of the components if they might be present as well.

And also how the pharmacokinetic model might capture some of the long term and chronic health effects that we know are associated with carbaryl exposure.

There is a number of built-in assumptions and extrapolations that to me as a naive reader seemed poorly supported. I'm listing a few of them here, but I want to red flag the issue in general.

The assumption that carbaryl is rapidly metabolized and eliminated might not be consistent with what we know about the chronic toxicity endpoints. Might not be captured, in other words.

There is no or poor data to support extrapolations from the bolus dosing that was used in the study, which was two oral doses, one hour apart, two toddler exposures, which are very different, 20 exposures per hour for two hours.

I'm not sure it is so easy to just divide those numbers and come up with something that describes the

toddler exposure.

The extrapolated carbaryl concentrations in the brain were from much lower doses. The extrapolated ones represent much lower doses. The data that was used to get those extrapolations were from doses that were much higher. The lowest one was, in fact, 25 times higher.

The model used the extrapolated brain concentrations to extrapolate the plateau level. I don't know much about these models, but to me an extrapolation of extrapolation raises a red flag for me already.

It is not to say that it is not valid, but it is to say that it is likely to be associated with a level of uncertainty.

Figure 2 is the graph that shows that. To me, it reads that there is built-in -- extrapolations built into extrapolations.

And the graph says that it finds a plateau reached after 90 minutes, but I don't think they had any data much under 90 minutes, only at two bolus doses.

There is also an assumption that the peak or plateau concentrations of carbaryl in the brain are

somehow a more accurate indicator of risk than the total absorbed dose.

I don't get that from the data and I don't see that supported in the document that was available for the public to look at.

So what would the public need to see to be confident or comfortable with the use of any model including this carbaryl pharmacokinetic model?

These are more general concerns that I have. How does one present this data to get public confidence. I want to talk about it in three categories, subjectivity, uncertainty, and transparency.

Risk assessment is not a science. I actually didn't know this until Dennis Hendershot (ph) at Rohm and Haas told me this a couple weeks ago. I'm quoting him there. And if he can say it, I think I can say it with confidence.

All risk assessment, according to him, is quantification of an expert judgment. I think that that's true. I think that that's good.

It is not something we want to pretend that

we're eliminating, that there are a number of expert judgments that go into many different stages of developing a model and a risk assessment based on that model.

There are possibly thousands of judgments imbedded within it. And I think we want to understand that and not pretend that what we have are absolute data or absolute numbers that are somehow infallible and without a degree of uncertainty associated with them.

All decisions are made under uncertainty. It doesn't mean that we need to delay our decisions. It doesn't mean that our decisions are invalid.

I'm not -- I certainly don't think that they are invalid. But I do think that uncertainty should be quantified. There should be some numbers there. We know it is there. How much is it.

Rather than presenting numbers or short ranges, this should all be associated with some kind of range of uncertainty and that uncertainty should be data driven.

We need an uncertainty analysis of each source of data, including all aspects of the model predictions, and a sensitivity analysis to compare the effects of the

uncertain assumptions. Which uncertainties matter the most.

Transparency. We should be aiming for developing the least complicated model possible. And integrate the model with an explanation and documentation of the assumptions.

I didn't see that -- didn't see any of that in the short document that was available for me to look at to prepare for this meeting.

I don't know if you were given additional information. But what was available that I got didn't list any assumptions. And it certainly didn't list any uncertainty or bounds associated with those assumptions.

And explicit uncertainty analysis can be informative and can help decide how simple or how complex the model needs to be made.

A systematic rationale for choosing one data set over another should be supplied and for quantifying the confidence in the data sets that are used.

Einstein says, a theory should be as simple as possible, but no simpler. That would really help the

public, I think.

In conclusion, question 1 talks about, asks the Scientific Advisory Panel to comment on the design of the pharmacokinetic studies.

The design of the studies to me seems inadequate to capture repeat exposure scenarios, the chronic effects that we know are associated with carbaryl, such as potential cancer effects, potential reproductive effects and the long term health effects that we see.

The design of the study seems inadequate to model the known chronic effects. The design of the study seems inadequate to model the full range of carbaryl toxicity, including possibly unreacted phosgene or other components.

Question 2. On your handouts, it may say blah, blah at this point. That's because when I wrote this, I didn't have the exact wording for question 2.

But I knew what the answer was. So that should be on your handouts, and it is the approach. Please comment on the pharmacokinetic approach.

In general, we do support the use of robust

pharmacokinetic data to inform risk assessments. Certainly we do. And the pharmacokinetic model, though, that I think is before the panel is inadequate to explain numerically the effects of the built-in assumptions. It is not a transparent model.

And the model does not include either an uncertainty or a sensitivity analysis that I was able to discern and does not attempt to provide quantitative estimates of the uncertainty.

So what we recommend is that the Scientific Advisory Panel recommend that the model include a list of built-in assumptions and quantitatively estimate the uncertainty and a sensitivity analysis.

Then this could either be used to inform the use of an uncertainty factor to accommodate the inherent uncertainty within the model or else recommend rejection of the model if that's not possible.

Thank you very much for your time.

DR. HEERINGA: Thank you very much, Dr. Sass. Are there any questions from the panel, questions of clarification for Dr. Sass on her presentation?

Not seeing any, I would like to put out one last call. Is there anyone in the audience who would like to make a public comment at this session?

That being the case we have made very good progress this morning and I think that what I would like to do as Chair at this point is to break for an early lunch.

And if schedules work, I am sure they should for the panel because they are a captive audience today, I would say that we reconvene here precisely at 1 p.m.

We will continue at that point with the panel's responses to the two directed questions from the EPA.

(Thereupon, a luncheon recess was taken.)

DR. HEERINGA: Welcome back to the Scientific Advisory Panel again on the topic of the use of pharmacokinetic data to refine carbaryl risk estimates from oral and dermal exposures.

I believe that we had concluded our period of public comment. But just to make sure over the lunch that there is nobody in the audience in the public that would like to make a comment on the session before we move on to

the directed questions from the agency.

Not seeing any interest, before we begin the questions, I think that I anticipate in talking to several of my experienced colleagues on the SAP that the discussion of these questions, while there are only two of them, it is going to be, I think, quite broad, quite heterogeneous in terms of our response.

What I would like to do is offer a suggestion to the panel. We have the afternoon to work through a response, appropriate response to these questions, that we make an attempt in our initial response to focus specifically to the directed questions and those components.

At the end of those two questions, as we always do, we will give everybody the opportunity to raise additional issues, scientific issues related to the question of the use of the pharmacokinetic data and these models in assessing oral and dermal exposures.

And that if you would use that period of time of general comment to make these points that you feel would be beneficial to the review of this particular background

paper and the modeling efforts that have been done and also to sort of the continued development of this methodology.

So with that, I guess, I would like to turn to Dr. Farwell and ask if he would read the first of the directed questions into the record.

DR. FARWELL: Charge question 1. Design of pharmacokinetic studies. A series of pharmacokinetic and metabolism studies were completed that serve as the basis for the proposed approach associated with children's exposure to carbaryl after lawn treatments.

These studies included dosing rats via several routes, oral, dermal and intravenous. In a subsequent study, carbaryl was administered to rats via the oral and dermal routes simultaneously at exposure levels similar to those calculated in the agency's deterministic exposure assessment for toddlers playing on treated lawns.

Question A. Please comment on the design of these experiments with respect to the usefulness of results to estimate peak tissue levels for risk assessment purposes.

Question B. The design of the multi route study was intended to mimic the concurrent oral and dermal exposure of toddlers playing on treated lawns. Please comment on this approach.

DR. HEERINGA: Dr. Reed is our lead discussant on this question. After her we'll move to the associate discussants and then open it up for comments by the full panel. Dr. Reed.

DR. REED: Can I get a clarification. Should we go ahead and address Question Number A first and then go around for that and then come back to B?

Or would you prefer that we look --

DR. HEERINGA: Yes. I -- let's handle it that way, if you want to do part A. They are distinct enough. Let's do it that way. Thank you, Dr. Reed.

DR. REED: There is some cross over, but I will try to sort them out.

First off, I think for building a robust set of data for refining exposure estimation, these two studies represent a good start to a different way of estimating the total exposure for use in risk assessment.

Some of the issues regarding the design of this study really has to do with how the studies or the data from the study is going to be used in risk assessment.

That comes to the second question. So for now, my comments would be confining to addressing the design of the studies for toddlers' exposure to lawn treated with carbaryl and only pertaining to peak brain carbaryl concentration and only from acute exposures. And that's a lot of sort of caveat in it.

I want to start with a very simple list. I'm sure my colleagues would have many other aspects and different depth into these comments and many others.

First of all, when I think of basic pharmacokinetic study, I'm thinking that it would provide me with sufficient data, with good quality of course, for deriving a fairly complete set of pharmacokinetic parameters.

Just to name a few, even though you were only interested in getting some information or having some data to predict the peak concentration, I will say that the basic set of parameters that I am looking for it is

something like peak concentration and data that would be sufficient for me to figure out what is the area under the curve.

I want to have a good complete time course and data that I could estimate a half life. It appears that many of these data are probably available from these studies, but they are just not -- presented in a way that I'm not sure if it is there.

The second layer of thought is that -- so that's the basic pharmacokinetic study. But for each -- to be able to generate data for risk assessment, I think -- I am looking for a complete picture from the point that a toddler comes in contact with this chemical all the way to when the chemical leaves the body.

And again, I don't think the full data is there. However, I cannot quite say if it is true, because -- actually, I have some difficulties or I spent a lot of time trying to just understand the studies in the way that it is presented.

And even after that, I weren't sure. I think judging from the questions that we asked this morning for

clarification, I'm not the only one who has some sort of questions about what the study is about in terms of based on its presentation of data.

So that may be something that needs to be worked on and get more clear, more focus on what is going on.

In using these studies to come up to -- to feed into the proposed model for calculating or for refining the toddlers' exposure, I felt there is actually very limited amount of information that is used in this regard. But then in that, there is also many assumptions that has to be drawn in into it.

And that's where, I think, in terms of data generation and design for a study you should look into that and make them more connected.

Several sort of minor comments. One is it is obvious with the first study that the detection limit was not high enough to detect brain carbaryl, I think, from the oral studies. The mix dosing study corrected that. So there is missing holes in the data collection from the first study because of that.

Some of the questions that I raised about being

able to -- the studies being able to address some apparent maybe discrepancies in the data that is not very obvious to me, things to address that would help.

I was concerned about if you want to use this set of data, the fasting versus food in stomach for kids, fasting with the rats, issues like that need to be brought in into the pharmacokinetic data for discussion.

I was also concerned about the size of the bandage compared to the children's surface area coming in contact with the lawn, playing in the lawn.

Not to say that the study was not designed right, but if you want to design studies for use in risk assessment, these issues has to be brought into discussion, both in the design and also the presentation of the data.

In addition to that, I thought it would be really, really cool if you are measuring the carbaryl concentration in the brain, that I could have looked at that cholinesterase inhibition data.

And also any cholinergic signs that were observed, given that it wasn't for the purpose of toxicity

study, but anything of that would be very useful.

Finally, I don't think the studies is designed for, and I don't think that was the intent, I don't think the study was designed for translating the biomonitoring data to peak concentration.

DR. HEERINGA: Dr. Reed, I wondered if you in the interest of the other discussants who may have integrated their comments, maybe whether you would like to go on to part B as well or do you feel that--

DR. REED: My part B is actually very short. I think the mixture study is good. But I think it is telling me that what I suspected would happen since we're focusing on peak concentration.

What I was actually looking for is some -- perhaps some design that would allow me to see where rate limiting factors might interact. And therefore, makes it different than separate route of exposure pattern.

But I understand that the purpose is to bring the dose down to very low level and so that interaction is probably not going to be very clear.

My second comment is that I appreciate the

mixture study or mixed dosing study because it adds a point to that, to allow you to do the regression between the TRR and the brain carbaryl concentration and that is a plus. It doesn't have to come out of a mixed dosing study.

DR. HEERINGA: Thank you, Dr. Reed.

Dr. Fischer, if you would continue with your comments please.

DR. FISCHER: I start off by agreeing that the concept of using data such as was accumulated here in risk assessment is very good. And I support it entirely.

I think this is a step forward that we have all been waiting for for a long time. So I'm hoping that what we're telling you will be beneficial in continuing to use this approach in risk assessment.

The design of the experiments as was pointed out earlier by the Bayer people could be better. It was their first attempt at doing this kind of experiment, they say. And they are learning a lot.

And I think all of us who do experiments know how the first experiment or an early experiment goes

compared to after you have done it for quite a while.

So things could have been done differently. I think probably they thought about it more than I have and know ways that they can improve it or could improve it if they so desire.

But I suspect that we have got to assume that we use the present data and carry on with it in terms of trying to decide whether it is useful in risk assessment or not.

The sensitivity, we don't -- let me stop and say that or start over again and say that brain levels were selected as the target tissue.

We just have to hope that that really is the case, that the brain is the true target tissue and provides the most sensitive measure of the effect.

I'm willing to accept that. But the possibility exists that it may not be, particularly if you are thinking about long term effect that may occur, not immediate sort of action.

So let's say we'll accept the brain. The problem is that we don't know the peak level in the brain

because the experiment didn't have short enough time points to detect peak.

So we don't know whether that peak was higher than the 15 minutes, I think it is 15 minute level that we call the peak. So I wish we had those values. And I'm sure everyone wishes that we had those values, but we don't have them.

How could they have been obtained? They said they couldn't measure them. But, in fact, in the beginning maybe the radioactivity, the activity, the radioactivity could have been much higher.

And they would have made it more sensitive and that could have detected carbaryl in the brain at very early times and then followed it out longer so it would have a longer time course than we have.

This increased sensitivity maybe you would be able to look at plasma and other tissues which might give us some additional information.

So there is no point in going through all the possibilities of improving the design. It wasn't the best, but it did yield some information about peak levels

in the brain.

So I think from that sort of harangue, you can tell that I'm willing to go along with using this data to approximate peak levels.

I'm pretty sure, but don't know why, that they are close to being what the peak level would be, that is, the actual data that we see at 15 minutes.

The focus on measuring total radioactivity that the results seem to have sort of throws one off. I know it threw me off in thinking that, well, my goodness, they are paying a lot of attention to total radioactivity, which we don't know what that is.

And maybe they are doing this because they think there is some metabolite in there that is very active and contributing to the effect.

I don't know whether that's true or not, but use of the total radioactivity in terms of understanding the kinetics of carbaryl, of course, is not a very reasonable thing to do.

It is a good thing that for the brain they did pull out the carbaryl and we can take a look at those

brain levels. But, again, I hope that we're looking at -- when we look at unchanged carbaryl in the brain, that we have got the right target organ and that we have got the right active substance in mind.

The only active substance in mind we have as carbaryl. Is that right.

Now the design of the multi route study. It is pretty -- when you think about it, well, we could have had carbaryl sprayed on some grass and then we could have put rat toddlers in there and watched what happened and made measurements.

But that wouldn't work either, probably. So what would be a good mixed dose experiment is anybody's guess.

I think there are probably a lot of them that could have been chosen. This one uses two oral doses and one dermal dose. Do I have that right?

MR. DAWSON: Yes.

DR. FISCHER: I think it is reasonable and okay maybe if one thought outside the box. They can think of a little different way, maybe a little better to do it.

But this at least puts oral doses on a background, so to speak, of a dermal dose, which is reasonable.

It is a case, though, that if you give 2 dermal doses and, in fact, you are trying to model 20 doses in there, the peaks after these two oral doses are going to be much higher than the peaks you will see if you had multiple low doses, so to speak.

So that the peaks are higher in this case and that might be wanted. So it could be on the conservative side. So I think the idea is okay.

It puts oral doses on a background of a dermal dose and it is sort of an accrued approximation of the possibility of the multiple dose that would occur in a toddler.

So I'm willing to go along with that and accept it too because I haven't dreamt of a better way to do it. I think that's all I can contribute at this time.

DR. HEERINGA: Thank you, Dr. Fischer. Dr. Pessah.

DR. PESSAH: I apologize if some of these will

be repetitive. I will try to summarize in a succinct fashion.

I think first of all Bayer CropScience should be commended for taking this effort to do a more refined risk assessment based on these kinds of models. I think it is a step in the right direction.

From my perspective, there were a few limitations in the design of the experiment. Probably the most fundamental one is that these were done in near adult rats rather than juvenile or toddler rats.

I don't buy the explanation that based on Padilla, et al., that this was a more sensitive model, because that particular study was looking at acute toxicity at rather high doses.

And so one wouldn't at all address the possible concerns of even what we're trying to do here, which was low repetitive chronic exposure.

There is very great variability in the metabolism of carbaryl in these rats. And this represents several other problems when one tries to translate this to toddlers.

Does the admae (ph) really reflect what might happen in toddlers exposed to repetitive doses. I think perhaps that would be one very big limitation in terms of extrapolation.

One thing that the rat doesn't do, and it is something that we're all confronted with, is whether or not genetic diversity has anything to do with ultimate toxicity. I think it does.

These rats showed quite a bit of variation in terms of pharmacokinetics and they are quite inbred. I think in humans you are going to have much more genetic diversity.

So I think that to answer directly part A, I think we missed the peak doses, so we're not really sure what the peak dose is.

I think some members of the panel raised the idea of doing the area under the curve or at least better model fitting to estimate what the peak might have been at very close times in.

And then moving to part B, is the dermal exposure appropriate. Again, I have to sort of defer to

some of the things that I heard from Dr. Stinchcomb that maybe the rat isn't the appropriate model for carbonate exposure. At least dermal exposure, that the guinea pig may be a better model.

I think the protocol is an oversimplification. It doesn't account for buckle absorption.

In many cases, it's not a direct transfer from hand to mouth, but from toys that are left out in the lawn which may accumulate higher levels of carbonate since most of them are absorptive in the type of substances that they are made of. It doesn't account, I think, faithfully for surface area.

I think that's all of my comments.

DR. HEERINGA: Dr. Stinchcomb.

DR. STINCHCOMB: I don't think there is too much new left to say. So I will just reiterate.

Early time points I think would be critical especially if there were early buckle absorption, which seems like it could be very significant.

But this was definitely a very good start at a pharmacokinetic study. It is great that all this work was

done. That's important to say too.

And just because I do have data on carbonates in particular, it is very odd that I have that data, but that is one compound where -- I was looking at the data, actually. In human skin, we get a four fold increase over -- we use guinea pigs, in human skin.

So that is a concern. Human skin diffusion studies are very easy to do. Just compare in the rat to make sure that that's a good comparison or what is the difference. That's going to be important to look at.

And I'm concerned that we don't know some of the toxicities of the metabolites. So we need to consider that. And maybe combine peak end area under the curve when we're considering what is important.

That's similar to what the FDA does. So if peak levels and area under the curves are important in direct dosing, it should be similar here for pharmacokinetics.

As far as the multi routes, it is still the same concerns, then, that the skin might have a significant contribution to the total absorption at the later time points that was pointed out by Dr. Bunge.

And I think that's pretty much it as far as the multi route study. But it is definitely a good simulation of what might be happening except for the early time points and the consideration that the rat might not be the best model for the dermal absorption.

DR. HEERINGA: Thank you, Dr. Stinchcomb. Dr. Bunge.

DR. BUNGE: Just to follow on what Dr, Stinchcomb said, the comparison of the guinea pig and the rat, I'm sorry, guinea pig -- rat and human, I should say, the comparison of rat and human in vitro to confirm that the rat is appropriate would need to be done with fresh skin. It is a metabolic skin difference.

A lot of my comments follow. I have a few additional details that might be worth considering. Like the other members, I support the general concept of trying to use a relevant internal dose metric to estimate the MOE. I think this is a strategy that is worth taking.

There are some issues of concern to us in this case, but I think it is a start in the right direction.

The main issues that I have is the issue again

of the peak concentration versus another dose metric, whether it is area under curve or something else.

Chiefly, because the conclusion about the effect and contribution that dermal will have or doesn't have depends on the choice of that metric.

So in a combined exposure situation, if it is the peak and it is not a very large dermal exposure compared to the oral, similar, say, to the case we got data for here, the contribution of the dermal could be neglected.

Whether that's the best and most conservative approach, I'm not sure. So I want to raise that issue.

The other issue that I think especially in future experimental designs of this type that really has to be watched carefully in these mixed exposure experiments is that the relative importance of those, the dermal and the oral, critically depends on the applied dose, the administered dose in the dermal on a per area basis. Not just the mass.

And if I want to translate the information from an experiment like this experiment to toddlers, I have to

do that -- I can only do that translation on an equal basis, both on body weight and skin area.

So just to put this into context in this experiment where I think the -- I have the numbers here, the -- it was .225. This was for the mixed exposure case. The applied administered dose dermally was .225 milligrams.

On the rat, that worked out to be .87 milligrams per kilogram or .017 milligrams per centimeter squared.

I have all these numbers for people to look at. I think those are the numbers out of your report directly as best I could tell.

That's because the area was 1 by 2 inch areas, 12.9 centimeters squared. If I take a 15 kilogram toddler, that would be 13 milligrams of administered dose that's equivalent because of the equivalent weight.

That would correspond to 757 centimeters squared of area. That would be a comparable area loading to the rat experiment.

That's the question. Is 757 centimeters squared the area that you would expect the child to be exposed to.

If the area is larger, so you have a 6,000 square centimeter child, and it is more like 2,000, then the actual amount that absorbs dermally could be larger than you estimated based on this experiment.

So that's the concern you need to be careful about, is to make sure that the ratio is relevant.

It probably wouldn't change the conclusion about the peak concentration in the brain coming from the oral because the dermal will still be delayed and will be probably a smaller peak unless you had a larger applied dose here.

It could, however, contribute to the area under the curve if that was a better metric. I think that's the issues I have to raise.

DR. HEERINGA: Thank you, Dr. Bunge. Dr. Wheeler is the next scheduled discussant.

DR. WHEELER: Thanks. Again, I think the overall approach to get away from administered dose and getting into an internal dose I think is, as a young guy, it seems common sense to me. So I haven't been around in this field so long that it seems like something that is

very common sensible to do.

And I understand the limitations in that. And so that leads me to some of the things, most of which have already been said, the problems with what I think we have discussed today.

I think a significant improvement would be to accurately determine the elimination rate or the half life as already stated.

And then to reiterate, since peak is certainly of most interest in terms of the toxicological effect and perhaps even a risk assessment, the peak is less defined and pronounced in the dermal exposure compared to the oral. And that makes almost the dermal absorption negligible in the mixed approach. So then I kind of question, that's kind of leading into part B. That leads to the question in that approach.

And then another important factor that was brought up this morning that we haven't really discussed yet is the notion that there may be differences in metabolism or at least elimination rate with respect to dose.

And if that's indeed the case, then that sets -- that maybe highlights our incomplete understanding of the metabolism or what is going on at the level of the tissue.

And then I think the important thing is that that may be an important factor not taken into account in terms of the subsequent calculations used to determine peak or plateau dose.

And actually, would lead to an under appreciated concentration, I believe. And I think the overall approach to assess peak can't be fully appreciated since we really didn't see peak in a lot of the studies and I think that's a weakness.

Finally, going to the approach of the mixed dose. I think if you want to -- so the approach using two oral doses, obviously, is more practical in terms of treating the animals than it would be than to give them 40 doses over two hours.

But if the goal is to see a steady incremental dosing, then I think a model of intra gastric gavage is actually probably more relevant.

DR. HEERINGA: Thank you, Dr. Wheeler.

At this point in time I would like to ask if there are any other members of the panel. I would like to begin with Dr. Handwerger.

DR. HANDWERGER: At the moment, perhaps later, but we haven't discussed at all the chronic effects. To me, that's an important issue. If, in fact, there is an increase in renal disease as Dr. Sass brought up, we're not even discussing that.

And clearly that's not going to be related to some change in an enzyme that occurs briefly and is gone in a few seconds.

And children aren't exposed to lawns for two hours and that's it for their entire childhood. Children are on lawns every day, month after month, year after year.

And there can certainly be an accumulated effect rather than acute effect over two hours. It seems to me that we have had no discussion except in the public comments about the repeated nature of exposure. And the fact that if there are chronic effects we're not even

looking at those.

Are people dying of renal disease as a consequence of this? If they are, we haven't examined, we haven't even heard the word kidney until the public discussion. So I'm really concerned about the relevancy of this entire discussion about the toxicity of this pesticide.

Because it may not be the acute things that are important. It may be the long term chronic complications.

Is there any evidence that people who are exposed to these lawns for 15 years, 10 years, have anything abnormal about their renal function or their lungs or anything else in later life.

I think those are important things. And it is not what happens 15 minutes after the exposure, but it is what happens 15 years after the exposure. And we haven't addressed that.

I don't think, I don't see how you can make a risk assessment on something that occurs acutely when we're looking down the line.

And what is the evidence that all of the

complications are related to this enzyme change? There may be -- certainly, I don't know of any compound that has a pure effect.

It could be affecting a variety of things. We just know about this one. What are the other effects? What is the pathologic basis for chronic complications?

We haven't discussed any of this today. So I don't understand how we can talk about risk assessment.

DR. HEERINGA: I don't think -- in all fairness I want to move on Dr. Perfetti, why don't you --

DR. PERFETTI: I can address that.

The Office of Pesticides Programs when we do risk assessments we do an acute risk assessment, a short term risk assessment, an intermediate term risk assessment and a chronic risk assessment.

Each one of those risk assessments may address a different endpoint. Very often they do. This pharmacokinetic approach applies to our short term risk assessment.

And we have determined the appropriate endpoint, the most sensitive endpoint for that short term risk

assessment is cholinesterase inhibition.

DR. HANDWERGER: Are you doing a chronic one?

DR. PERFETTI: We have done a chronic one on this.

DR. HANDWERGER: What were your conclusions?

DR. HEERINGA: I would like to turn -- I think our focus here is on the pharmacokinetic modeling.

I think we're going to get to some elements of your point in responses to question 2A as well. I would like to move on at this point. Dr. Edler.

DR. EDLER: Just a comment to the designing of the mixture study. I think it has been said that it is a good step to go into the mixture looking for oral and dermal.

But I think if you go into the mixture, you have all these problems, how to design the whole study.

It might be considerable that you also then have a group, maybe a group which you don't have so intensively studied but at least for a couple of time points where we have only the oral and only the dermal just to get more information what is going on.

I don't want to speak about interaction at this point, but I think the methods are so different. The kinetic styles are different in the two. But anyway, you will learn more about that.

DR. HEERINGA: Dr. Hattis.

DR. HATTIS: I want to add. With response to the question, too, I'm going to argue that you really ought to be focusing on the cholinesterase inhibition and you can do that approximately by modeling.

But I also want to point out that if you really were interested in the peak carbaryl brain concentration as you have done, you can at least bound what that could possibly be by straight forwardly projecting back from the existing data that you have.

And the answer is that if you have a 15 minute half life for carbaryl, you can't get more than about two fold from the 15 minute observation back to the initial observation.

So I would -- because the assumptions to the modeling analysis are that you get essentially instantaneous absorption and distribution to the brain,

you can reasonably comfortably make that back projection to 0 time and say we couldn't be to -- we're probably overestimating a little bit, but we probably are not far off by making that kind of assumption.

In fact, there probably will be a finite amount of time for the absorption and distribution to the brain.

So you could make other assumptions if you wanted to be a bit more refined about that based on other information you might have available. But it is a soluble problem.

And the only way you could really go wrong that way is if there was, in fact, a super fast elimination phase right at the beginning that you completely missed.

I think that's formally possible. You can't be absolutely sure you are being conservative by a twofold increase, but you wouldn't -- but I think it is reasonable to do that projection from the existing data at 15 and 30 minutes.

DR. HEERINGA: Thank you, Dr. Hattis.

Dr. Riviere and then Dr. Brimijoin.

DR. RIVIERE: I just have two very brief

comments to make sure they get in here for -- in designing future studies.

One, I want to reiterate what Dr. Bunge said that when using mixed exposure study, it is really now fixed by the surface area ratio of the rat to what the upper limit would be for the surface area exposure ratio of the humans.

And that's the problem of not doing the study separately. Because if you did them separately then you could normalize the surface area and extrapolate.

But since your observation is dermal and oral, you are sort of stuck. So as long as that extrapolation is remembered.

Secondly, we didn't talk much about the actual method of application. Just to reiterate. This carbaryl was applied in this aqueous acetone vehicle where the acetone was supposedly evaporated, but I'm not sure that was actually tested.

In the future, it is not that if it was a solution of water sitting here with acetone in it, maybe, but there is a plastic waterproof bandage.

And acetone probably would love to go into that bandage. You are actually looking at a partitioning of the acetone and/or the water and/or the carbaryl into the bandage and the bandage material.

Again, that really determines what these responses are. That may not be the same as what happens in the human exposure ratio.

DR. HEERINGA: Dr. Brimijoin.

DR. BRIMIJOIN: I'm still thinking this through. I apologize. I'll make it brief. I want to get these comments in because some version of them will probably find their way to the written report.

So I'm starting from the standpoint that although there may indeed be other toxic consequences of exposure to carbamate, that a common mechanism of toxicity is cholinesterase inhibition.

And so the measures of exposure, peak exposure are relevant only insofar as they help us predict what will be happening to that locus.

I mean, that's my starting point. If I'm way off base, maybe the chair can stop me right there.

DR. HEERINGA: No. You are fine. I think it is an important point for the audience here too that anything that goes into the final report, the minutes of this meeting, has to be expressed publicly in the course of these meetings. So please continue.

DR. BRIMIJOIN: So starting from that point, then, as I listen to all this and read all these documents, I have been thinking how does this data help us predict what would be going on at the target enzyme site.

I appreciate the experimental difficulties and the reason for choosing the brain now as the solid tissue to measure drug or agent levels in. It was really the only probably source that you could measure active carbaryl.

So that's fine. At least it is a starting point, even though it might not be the most relevant tissue.

Now, the problem is that when we're going -- what we really want to go to I think is not -- it is ultimately the peak predicted levels of brain cholinesterase inhibition.

And that's why we're trying to estimate what the actual levels of the compound are in the target tissue. And the problem is that the data may be there, but they haven't been analyzed in a way that fully takes into account the fact that the half life of the inhibition itself is about eight times longer than the computed redistribution half life in any way of the carbaryl.

We were told that carbaryl clears from the brain, the alpha parameter, indicating a half life of 15 minutes, whereas we have a couple hours in humans, nearly three hours for the apparent until you have to recovery.

So that's particularly relevant in the case where we're trying to model -- we're going from a single or dual exposure model paradigm to model a human exposure that we're thinking might be repeated over clusters, very short periods of time. Just a few minutes.

And so what could be happening is -- it is easy to see if the residence time on the enzyme itself were, let's say, infinitely long, then that would be the only factor to consider.

We would just simply add the levels of inhibited

enzyme in each step. It is not that bad.

But we have to somehow introduce into the analytical part of this model something that allows for the fact that there is a potential for substantial cummulation of drug effect that will peak at a later time and a higher predicted level than you would get from any single exposure.

That's my main comment.

DR. HEERINGA: Thank you. Good point. Dr. Hattis.

DR. HATTIS: I would just inject here that I could show a slide showing that exact point later, but I could show it sooner if you think that would be better for --

DR. HEERINGA: I guess I would prefer, if you would like, we will keep this in mind and keep it in the order you had originally intended to present it.

Dr. Chambers.

DR. CHAMBERS: I would like to reiterate some of the comments that were made earlier. I think this is a very good approach for dealing with compounds that are

very metabolically labile and have very quick effects in the body and is reactivated readily.

To comment on the fasting comment that was made earlier, by fasting the animals, I think you are getting a more conservative estimate of absorption.

I think that was probably the reason for that. It was a good idea. If the animals were not fasted, that would have probably slowed down absorption quite a bit.

And then with respect to the brain, if there is ever any attempt to correlate the levels of carbaryl with cholinesterase inhibition, since that is the target, then the brain is really about the only practical target tissue to assay.

Again, that makes a lot of sense that that was done. The peripheral tissues -- well, the blood, of course, is not a target tissue. The peripheral tissues that might be considered a target tissue are extremely difficult to assay.

And to get reliable results from that is something that reactivates as quickly as carbaryl cholinesterase probably would not have been a practical

thing to do.

So I think the brain makes a lot of sense as the target tissue to study here.

DR. HEERINGA: Dr. Kehrer.

DR. KEHRER: I had three points I wanted to make or maybe get some more input from some other members of the panel because some of these relate to things that were said.

Several panel members talked about using area under the curve as a different metric to try and deal with this. But there may be ways to use that to refine the peak levels.

If you use area under the curve, aren't you just looking at total dose, which is where we are now? And that doesn't sound like we're moving forward if we go that route.

The toxicity of metabolites is something that doesn't concern me in an acute sense. Carbaryl has been around and is widely used in metabolism.

It clearly doesn't make metabolites that are worse in carbaryl in the acute sense. Chronic is a whole

another issue which we're not dealing with today. So I don't want to get into that.

Then I wasn't convinced with this dermal exposure ratio issue that somebody brought up. I don't see why it needs to be comparable between the rat that was used as a model and the toddler.

The rat is going to be exposed to a constant amount over the entire surface area that is exposed. The toddler is clearly not. It is going to be variable over the whole thing.

In the end, what you are looking for is something that is comparable in terms of a total dose that's being exposed to. I don't know that having comparable surface area is going to accomplish that.

DR. HEERINGA: Thank you, Dr. Kehrer.

Dr. Bunge.

DR. BUNGE: Maybe I could comment on two of the issues, the last one first.

Absolutely. The toddlers, we don't know what the actual dose is going to look like, the exposed dose.

But for a given dose, if it is applied over a

much larger area or they get it over a much larger area of the skin, the amount that absorbs will be more proportionally than it would have been if it was over a smaller area of the skin.

So that's the issue. Is the area that the rat is being exposed to for the dose they have relevant. It is the mass per area that matters in the rat experiments, not the mass per body weight issue.

And the problem is when you extrapolate to low doses, this is one of those examples where the amount that absorbs on a percentile basis increases as you go down in dose.

The extrapolation isn't conservative. So that's the issue there. I would say that the area under the curve isn't the total dose if it is being measured at the target tissue.

So if the dermal dose, for example, is going into the body at a slow enough rate that the body is metabolizing it very rapidly and it is not even making it to the target tissue, the area under the curve at the target tissue won't be the same as the total absorbed

dose.

I think they are distinctive. I don't know which is the most appropriate way to do it. Peak concentration or area under the curve.

I just raise the issue that in this case it makes a difference in the conclusion about whether the dermal absorption is contributing when you are doing the risk assessment or not.

Just one or two other comments that I forgot to make earlier. I want to get them on the record. With respect to is this the best design, this combination of oral and dermal at the same time, I'm not sure what the right answer is.

The advantage of it is that with the same number of animals, getting information on both the dermal route and the oral route simultaneously.

It might have been nice to have the combination compared to just the oral because then you could see what the real dermal effect is or maybe you just do the oral and the dermal separately.

The combination always leaves you with some

questions. And it always will put you in a situation in the dermal side that the relevant loading or mass per area will be restricted.

The conclusion from the experiment will be restricted to that mass per loading unless the mass per loading goes up.

If the child is on a mass per area base, it's likely to have a higher dose. Not necessarily total higher, but the mass per area is higher, then extrapolation is probably likely to be conservative.

If it goes in the other direction, mass per area is smaller potentially in the child than was in your experiments, then it may not be conservative.

DR. HEERINGA: Dr. Lu.

DR. LU: I have to say it is good to sit here to have a dialogue among the agency, the registrant and the panel members. I kind of sorted out the questions, the Number 2 questions.

I looked at question Number 2A and 2B, which is very similar to question Number 1, 1A and 1B. But I guess that EPA want to ask differently in terms of how to

use this peak concentration in risk assessment and/or exposure assessment.

I have to say that conceptually speaking, I think it is a good approach to look at the target side for the risk assessment purpose.

So I have no problem using peak concentration for the risk assessment purpose. However, if you look at the exposure assessment, if you look from the perspective of exposure assessment, we are talking about a target side which has no accessibility at all to the exposure assessment.

It is very unlikely, almost impossible you will get a sample of oral concentration from kids.

That's why Bayer has to interpret the results from peak concentration in plain (ph) and then do a mixed dose model and then use the number to calculate the MOE basis on peak concentration.

All of a sudden, we have to convert, we have to modify by 20, which is a big jump from the basic, the good approach to the very uncertain approach. And that really kill the proposal you have to say.

If I were Bayer, I would focus on what is known right now, which is just look at total absorbed dose and look at how we can convert one naphthol concentration in the urine over the long period of time.

And see how we can come to this more reliable MOE calculation. Otherwise, this peak concentration would be only good for the purpose of risk assessment.

But we will never reach to the risk assessment arena until we have a very exposure theater, which I don't think you would be able to accomplish to collect those good exposure assessment datas.

Part of the reason is I also want to talk about mixed dose models. I can understand why Bayer wanted to do this mixed model, mixed dose model, because you want bring this peak concentration plan (ph) to the urinary biological data.

By doing those calculation, based on some very simple mathematical calculation, not pharmacokinetic calculation, as I criticized in the morning, this graph which shows that after 90 minutes you will be able to reach a steady state, the plateau, peak concentration, I

will be very interested to see how you validate this curve.

One simple approach. Again, that's my criticism to the lack of the pharmacokinetic analysis is that you can model this curve at the moment -- say you turn off the input of the dose. See whether the decay curve will be the same as the curve that you show from the mixed dose model.

If that's the case, then you probably have a good standing on arguing that peak concentration would be good approach.

But without that, I wouldn't be able to conclude whether that's the right approach or not. That's something that I would emphasize.

In terms of the question 2C, I really don't know how to comment --

DR. HEERINGA: Dr. Lu, we're really on question 1, and I would prefer to hold your comments.

DR. LU: That's it.

DR. HEERINGA: At this point, I want to make sure, I think people are eager to get on to question 2. I

am as well. I want to make sure we wrap up question 1 first.

Are there any additional comments specifically related to the design of these two studies, and then we'll have ample time for the discussion of question 2.

Dr. Reed.

DR. REED: I want to clarify my concern about the need to address the fasting versus the real scenario of kids having food in their stomach.

I recognize that it was fasting. And again, as I said this morning, it is a standard protocol to dose these animals, fasted animals.

What I was concerned about wasn't that the peak is more conservative with fasting, but that when we are getting to this scenario we're looking at two routes interacting or in some way merging together.

I think there is a conclusion at the end to say that the oral route -- that the peak of oral route does not merge or come in the same time as the dermal, blood.

I'm saying if you have food, then the picture would be different. And that needs to be addressed. Maybe

the peak will not be as high, but it will be kind of a -- smooth out a little bit and maybe move over to the right.

I don't know what it looks like. But it needs to be addressed. I wasn't talking about just the peak being higher or lower.

DR. HEERINGA: Thank you, Dr. Reed.

At this point are there any additional comments that we want to make specifically on question 1. I think we have a chance to return I assume during the discussion of question 2.

Not seeing any, I would like to turn to Dr. Farwell or Mr. Dawson to see if they feel satisfied at this point. Are there any clarifications they would like to ask of the panel on this question?

DR. FARWELL: We're satisfied.

DR. HEERINGA: Let's move on, then, to question Number 2, which I think will stimulate some discussion here.

Dr. Farwell, if you would be willing to read the question into the record, please.

DR. FARWELL: Question 2. Pharmacokinetic

approach. Historically, risk assessments completed by the agency have been based on comparison of endpoints associated with total administered dose levels from toxicology studies with daily human exposure.

The proposed pharmacokinetic approach presented in this paper instead relies on the use of peak internal dose at the target tissue.

Because of the rapid pharmacokinetics and pharmacodynamics of carbaryl, a more appropriate dose metric may be the use of peak target tissue levels for calculating exposure estimates instead of total daily absorbed dose values.

Question A. Please comment on the appropriateness of using peak levels for estimating exposure.

And question B. This pharmacokinetic approach assumes that toddlers put their hands in their mouths at a rate of 20 times an hour for two hours.

A laboratory dosing regimen that exactly mimics this toddler behavior is impractical. As such, oral doses were administered in the multi route rat study once per

hour for two hours.

The proposed approach uses an algorithm to adjust the results for two hourly bolus doses to that of a toddler which occurs 20 times per hour.

Given the rapid metabolism of carbaryl, please comment on whether this algorithm can be reasonably used to predict the expected pharmacokinetic behavior of carbaryl.

And question C. To convert the four 24 hour time periods in the biomonitoring study to a shorter time period and to account for plateau tissue concentrations, Bayer has proposed extrapolating results from the rat mixed dose study to the biomonitoring study in this manner.

Because the margin of exposure calculated using estimated plateau brain concentration was approximately 20 fold greater than the margin of exposure calculated using EPA's SOPs for residential exposure assessment, Bayer proposed multiplying results from the biomonitoring study by an adjustment factor of 20.

Please comment on whether this approach is

appropriate for extrapolating from results in the rat pharmacokinetic study to the biomonitoring study.

DR. HEERINGA: Thank you very much, Dr. Farwell.

While there are several different questions being asked as sub parts of this question, I think in the interest of allowing the discussants to stay with their prepared comments, I think if you want to address them in full and then we'll return individually as we need to.

Dr. Edler first, please.

DR. EDLER: So we go through A, B, C, step by step. Right?

DR. HEERINGA: If you want to do all three at this point --

DR. EDLER: I don't want to.

DR. HEERINGA: Let me ask the panel at this point, just nods. Clearly, question A, I think, can be separated in part from questions B and C. Why don't we address question A first and then we'll systematically go through the group on sub part A and then we'll return to B and C.

DR. EDLER: Question A. I think it is just a

peak level for exposure. This is a question on just one point, the use of the peak concentration and primarily the peak concentration in the brain, as I understood that.

So it is a question on exposure, not on the toxic endpoint. The toxic endpoint would be the ChE inhibition.

What I found is that the peak levels have been used as dose metrics. And actually, I found two sources. One is the recent formaldehyde discussion where peak levels in the NCI study has shown the best correlation actually between exposure and effects.

So it is not -- they had peak levels, cumulative dose, average dose, and duration of exposure and peak levels actually are pointed out as a very relevant endpoint -- not endpoint, exposure measurement for getting to the endpoint. It is also an inhalation thing.

Then another thing is when we go back to the discussion we had last year, we had also a question on the response side, namely, the cholinesterase inhibition.

And there we have the peak inhibition as an endpoint and we had talked also about the length of time

above predefined inhibition.

I think this could be actually something in between the AUC discussion we had here and the peak level. So you ask for how long does the curve stay over a defined level. So it could be just a combined measurement.

What we had already here is that peak is difficult to find. That's clear in all kinetic work. Of course you can model it.

I think that's for the moment my comment and I will now pass over this to the other colleagues.

DR. HEERINGA: Thank you very much on this part. We'll return to you for B and C.

Dr. Hattis, please, sir, on part A.

DR. HATTIS: Well, on this part A, I want to say that fundamentally it doesn't make sense to focus on carbaryl concentrations in the brain, on peak concentrations in the brain rather than brain cholinesterase inhibition.

This is particularly true because very short half life carbaryl itself is the same point that, in fact,

Dr. Brimijoin, I believe, has already made.

He said that the MOE calculation that's been proposed to be used as substantive essentially comes -- gives rise to a larger margin of exposure that's permissible because of the idea that the different three minute separated doses don't interact very much.

But if, in fact, they are leaving behind the residue of the cholinesterase inhibition, it can be shown -- and that has a half life of the order of either 1.7 or three hours, that will cause the inhibition level to build up much more than the carbaryl itself will build up because the carbaryl itself only has a half life of the order of 15 to 19 minutes.

This calculation is the basis of the focus. The answer to question A is peak level of cholinesterase inhibition makes sense. I think that there is a case to be made for some other metrics as well for ultimate risk assessments.

But certainly, peak levels would be expected to be the main causal factor in short term cholinergic responses that are central nervous in origin.

There may be other things, but if it's central nervous system short term responses you want, I think that peak levels in the brain of cholinesterase inhibition, but not of the carbaryl itself makes sense.

And I have some slides to illustrate that, if I can get them on screen.

It was very nice of the sponsors to provide the actual spreadsheet that was used so I know exactly what was done to model the peak levels.

And that's the line that you see that was exactly the same as the line that was presented by the EPA folks.

Essentially, with doses every three minutes, you get bumps in the carbaryl concentration in the brain that then decline with a half life of 15 minutes -- or 19 minutes in this case.

And you see the buildup that tends to approach a pretty decent plateau after two hours, because that's approaching three or four half lives. And you don't get too much more after that.

But if, in fact, you have a buildup of a

cholinesterase inhibition that has a half time for reversal of three hours, that's the blue line at the bottom, and you can see that it is still rising rather steeply at the end of a two hour point.

So I think that would cause a substantially different MOE calculation if, in fact, you did on the basis of the expected cholinesterase inhibition.

Because the different instances of the three minute exposures, their effect persists for a lot longer than is implied by the 15 minute half life of the carbaryl itself.

This index of cholinesterase inhibition is the most simple minded thing in the world. Basically, it just says I'm going to -- at any one minute of time the average concentration of carbaryl in the brain is going to be counted as one unit.

And then I'm going to decrease the total accumulated amount of inhibition with a three hour half life thereafter. So this is how that accumulates.

And if you continue the every three minute dosing over eight hours, that's the next slide, you see it

continues to accumulate and you are still rising somewhat after even an eight hour period.

Now, this is of some significance because over that kind of time scale your four hour delayed peak dermal would, in fact, have some chance of contributing to that cholinesterase inhibition level.

I don't know how much it would contribute depending upon the relative doses and the amount of absorption, but it would tend to make some greater contribution than you would find if you were just looking at the brain carbaryl levels.

And this can be done directly on the same spreadsheet. It is really simple.

DR. HEERINGA: Dr. Edler.

DR. EDLER: The blue curve is a little bit delayed. Is that very natural?

DR. HATTIS: Yes, it is basically just the fact that you build up the carbaryl levels a bit. And then, essentially, the slope of the blue line relates to the instantaneous level of the carbaryl, which you see is going up.

When the carbaryl levels starts to flatten there, you will see a kind of an inflexion point in the blue curve.

DR. HEERINGA: Dr. Brimijoin, another question on this graph.

DR. BRIMIJOIN: Just a question for Dr. Hattis. So that explains the slope, the shape of the blue curve. But what do you have to say about its absolute positioning?

It is arbitrary. Right?

DR. HATTIS: That's arbitrary.

DR. BRIMIJOIN: It could be 10 times, 100 times, 10 percent.

DR. HATTIS: Yes. It depends on what units. I have just taken the units of carbaryl PPM in the brain as my -- because I don't know the absolute conversion between carbaryl and the brain and the rate of cholinesterase loss.

I can't express it as a percent. But if you were to calibrate it against some observed levels of carbaryl -- of cholinesterase inhibition at some time

point, then you could go ahead and express it in terms of percent inhibition units.

I couldn't do that from the data that I had.

DR. HEERINGA: Go ahead, Dr. Hattis.

DR. HATTIS: I'm done. All done.

DR. HEERINGA: Thank you very much. Just to clarify this last point, I think I understood that, but sort of being the simpleton here so that we can get the lay view on this, that you essentially took a standard unit of conversion between carbaryl concentration and efficacy with regard to cholinesterase inhibition.

DR. HATTIS: Yes.

DR. HEERINGA: That curve, its slope would have to be determined by essentially what that inhibition is, if it, in fact, were linear unit per unit as opposed to dose dependant.

DR. HATTIS: Yes. I'm assuming just first order interaction between carbaryl concentration in the brain and the acetyl cholinesterase molecules.

I think that's reasonable. I don't think there is any reason to believe that there is a funny behavior in

that function.

DR. HEERINGA: Dr. Brimijoin.

DR. BRIMIJOIN: I would like to say I think this is totally reasonable. And it is really the precise formal and elegant representation of what I had on my mind.

Probably from the levels that have been calculated with this HVLC mass spec assay, in this particular experiment, there may still have been immeasurably low or very difficult to measure levels of inhibition.

When you convert parts per million into probable molar units, which I like to see, I think we're down the nano molar range.

On the other hand, it is a quasi (ph) reversible inhibitor. So you take some experiment or careful model in to calculate it.

It may be that the real inhibition in this experiment was indeed very low, but that's not really the issue.

The issue is that this is -- the blue line is

the, in my opinion, and apparently in Dr. Hattis' opinion, the kind of thing we should be modeling toward.

DR. HEERINGA: Thank you very much.

Dr. Harry.

DR. HARRY: This is the other naive question.

These are assumptions, but you are working basically with no data because the levels that these doses were expected to be so small that you really could not detect them.

If you went back and you did the study with higher doses where you knew you could get a detectable level to see what the dynamics were, would you have changed the dynamics so much by increasing the dose with doing that?

Do you think you could do that or would that be something to give you the data, then you could back extrapolate?

DR. BRIMIJOIN: Can I answer?

DR. HEERINGA: Absolutely, Dr. Brimijoin.

DR. BRIMIJOIN: I think the answer is, yes, you could back extrapolate. Over the lunch break, I was

actually raising the possibility.

I mean, I have talked a lot and frequently at these meetings about looking at model -- at a variety of tissues, not just brain.

And actually, if I can possibly manage it, I'm going to get some data along those lines. Or maybe somebody is already doing such experiments at the EPA somewhere.

But I think we need the data. But I think, yes, it would be appropriate.

DR. HEERINGA: The next discussant for this particular question after Dr. Hattis is Dr. MacDonald.

DR. MACDONALD: This is really all outside my area of expertise, but from what I have seen, I would say that use of the peak is an interesting idea. But we're certainly -- it is worth exploring, but we're certainly nowhere near able to say whether it is a good idea or a bad idea.

DR. HEERINGA: Thank you, Dr. MacDonald. Dr. Riviere.

DR. RIVIERE: I thought of this question from a

pharmacokinetic perspective and not a pharmacodynamic perspective because of actually influence by discussions earlier this week about the difficulty of measuring cholinesterase levels.

So looking at this data from a way of what I think that the registrant was interested in, which is extrapolating across studies, then, if you are actually looking at carbaryl peak concentrations in a specific tissue, you know what you are looking at and you can have some sense of measure in that.

With that in mind, I think the use of peak internal dose is a good idea in a target tissue.

For rapidly acting compounds such as carbaryl, well, apparently, I understood a rapidly regenerating cholinesterase enzyme that it's primary target, the peak concentration might be the best.

It may not hold for other type of endpoints. Definitely for more chronic effects when the area under the curve might be more acceptable.

The problem with determining a peak that became evident in this study is it places additional constraints

on the design of the experiment because you need to actually determine where the peak occurred.

We know in this case maybe the peak occurred before 15 minutes. I think the simple back extrapolation based on that half life would give you the worst case scenario.

The second aspect is this is nothing new in a pharmaceutical arena, peak concentrations or fractional area under the curves, which is another approach of looking at that. Basically, the fractional area to pick up where you think the peak is and everything earlier than that would be another way to allow extrapolation across those studies.

The final thing that I think needs consideration is that if this is based on total carbaryl residues or total radioactive residues, then the route to route extrapolation may have problems. Because there were some situations. I believe the methyl metabolite was only present in the oral dosing, not the dermal dosing.

So depending on what the actual endpoint of that is on total residues. You are probably getting the worst

case scenario, which is what you want to do, but specifically to the active compound you may not.

DR. HEERINGA: Thank you, Dr. Riviere. Dr. Brimijoin, you are next, but I think if --

DR. BRIMIJOIN: I had my say. Thank you.

DR. HEERINGA: You are welcome to come back at any point. Dr. Lu, I think --

DR. LU: I agree with Dr. MacDonald's comment that this is more like a research topic rather than it is a done deal.

I think using the peak exposures -- peak level, especially for exposure assessment, remain to be seen in terms of how you are going to extrapolate those numbers to the final end stage of risk assessment model.

To me, what it presents here is really simple and not sophisticated enough.

DR. HEERINGA: Thank you, Dr. Lu.

Dr. Kehrer.

DR. KEHRER: Well, I will end up on a bit of the opposite side of the fence here, I guess. As I read this question, it was, comment on the appropriateness of using

peak levels for estimating exposure.

I have absolutely no problem with that. I think it provides a nice estimate of exposure. The question seems to be coming does it provide a nice estimate of the effect that is going to be seen with the compound.

And it wasn't -- that's not what the question was, but, obviously, that's the real thing you are concerned about with regulatory questions that have to be answered.

And there are some issues that have been raised with this. Does it estimate the effect of carbaryl particularly with the graphs that were up there. Those are very nice and clarified some things for me.

I have some concern with that. And the other concerns have been raised already about the lack of information on peaks.

DR. HEERINGA: In terms of its effect cholinesterase inhibition brain tissue, do you view that --

DR. KEHRER: Do I think the peak levels provide

-- I think it can. I'm not sure we're quite there yet, but I think they have gone a long ways. I'm not sure they have gone the whole mile, but maybe seven eighths of the mile from my point of view.

But there are some unanswered questions. And perhaps the data are there and they just need to do some more statistics. Of course you can get any answer that way.

DR. HEERINGA: Thank you, Dr. Kehrer. Are there any additional comments that panelists would like to make on question 2A?

Yes, Dr. Edler.

DR. EDLER: I just tried to summarize yes and no, I think. I think overall what I understand the discussion on this question is that we really have to go into pharmacokinetic and pharmacodynamic modeling at this point.

Because we're talking about the kinetic part. And exactly with this blue and black curve, we're talking about the pharmacodynamic part.

I think that might be the final end of the

story. But that's surely a long way to go.

DR. HEERINGA: Dr. Reed.

DR. REED: I just want to reiterate that I could tell you that when I was reading the report and it says that the part of the sample were parted out for cholinesterase measurement, and I jumped and I thought great, well, we haven't seen it yet.

DR. HEERINGA: Before we move on to part 2 B, I want to turn to Dr. Farwell or to Mr. Dawson to see if you seek any clarification on the panelists' comments.

DR. PERFETTI: I think Dr. Lowit has something.

DR. HEERINGA: Dr. Lowit.

DR. LOWIT: You didn't ask me.

Can you put Dr. Hattis' thing back up? I have a couple questions before we move on -- about that.

They reiterate some comments that Dr. Brimijoin had asked. Regarding the scale on the right side, can you explain that one more time?

DR. HATTIS: For every minute, I basically took one unit, essentially, of cholinesterase inhibition. And this is an index, not an absolute measurement.

But, essentially, what we're saying is that each minute we get 1 PPM brain concentration's worth of cholinesterase inhibition.

And then the next minute we get another unit from the -- according to the -- so I basically just multiplied the concentration times that one minute time repeatedly to get each minute's increment to the inhibition.

And then each minute I also decreased the amount of inhibition by approximately one 180th of -- one-half of 180th of the amount of inhibition that was present in the previous minute.

DR. LOWIT: Just to clarify to make sure that I understand personally, that the right -- the scale on the right is not predicted inhibition.

DR. HATTIS: It is an index of inhibition.

You could calibrate it to it if you had an observation for some particular dose at a defined time after administration.

You could calibrate that to the real percent inhibition.

DR. LOWIT: Let's say, for example, data that we do have, we do have the cholinesterase inhibition from the studies used for the NOAEL and the LOAEL that provided the basis for all of these data.

You could use those to then back calculate what it would be.

DR. HATTIS: Yes. The only difficulty you would get into is that percent inhibition is maximal at 100 percent.

You can't get more than that. If you have got measurements at very, very high doses where you get 90 percent inhibition, that's not linear in that time frame.

You have to -- but Woody Setzer (ph), as you understand, has done wonderful analyses with the OPs.

DR. LOWIT: And he will be back in February. We will talk about this more.

DR. HATTIS: His model will do well at mating with that.

DR. LOWIT: I want to clarify one more thing. The basis for the studies that were used in the mixed dose started with the -- if you remember the oral studies, the

low dose is 1 milligram per kilogram where there is no measurable cholinesterase.

Let's say it is arbitrarily at 5 percent. That's a reasonable arbitrary number to draw.

DR. HATTIS: Yes, Which is what you were doing in your head.

DR. LOWIT: If 1 percent or 5 percent is the maximum from that study, you are actually down extrapolating several times to get at sort of the toddler exposure.

So it is going to be probably several fold lower, if not orders of magnitude lower, than the five percent.

DR. HATTIS: Right. The margin of exposure would be to a defined percent. How much less dose -- how much more dose would I need to get to a defined percent inhibition.

DR. LOWIT: If the 1 milligram per kilogram is something that we can barely detect now, we're going to extrapolate probably in order of magnitude maybe two orders lower than that.

DR. HATTIS: Right.

DR. HEERINGA: Dr. Lowit, is that sufficient?

Dr. Chambers.

DR. CHAMBERS: Following up on that, though, I think your extrapolation here, Dr. Hattis, though, is on the parts per million in the brain.

DR. HATTIS: Right.

DR. CHAMBERS: And the data you are talking about having cholinesterase inhibition for is probably just over all administered dose, isn't it.

So you couldn't make this extrapolation.

DR. HATTIS: It would be better to make the pharmacokinetic model to make that conversion.

DR. LOWIT: I'm talking about pulling data from a couple places. The 1 milligram per kilogram was used in the -- not the mixed dose study, but the other metabolism studies that I think you have the copies of the single route.

That's the one milligram per kilogram. The basis for that comes from a traditional toxicology study.

So we have cholinesterase inhibition at

administered dose of 1 milligram per kilogram. We also have from that study the brain concentration enzyme.

DR. HATTIS: My preference is usually to make a projection like this from an effect dose rather than from a no -- an assumption about a no effect dose.

Basically, I like working with data that I have some measurement on.

DR. HEERINGA: Dr. Hattis' graphs will certainly be incorporated in the final minutes of this meeting as well. Any other questions or points of clarification on question 2A.

We can move on. Turning to Dr. Edler for question 2B, and I will leave it to you as to whether we do B and C. I would propose that we try to do B and C.

DR. EDLER: I think so. We'll have our first round and then we'll go to further questions as we did it just at the moment.

Again, the question was at the B. I will now give two comments on the B and C and then we'll go further.

The B question was given the rapid metabolism,

please comment whether this algorithm is reasonably used to predict the expected pharmacokinetic behavior.

And this addresses the mixed study where you have this one single group of rats, two bolus oral and one dermal, which has been discussed. And this study is supposed to mimic the toddlers.

We have this .15 milligram per kilogram orally and .75 dermally. And we are actually asked here only this one aspect, namely, whether the used algorithm is able to predict this PK behavior.

Before that, I think whatever we do here, it is a pharmacokinetic modeling. In this case, when you look in the document it is very, very simple.

It is just first all the kinetics. And it just comes up all to linear calculations, which has been done with a spreadsheet. Anyway, if you do this modeling you have to ask yourself what is the model, what are the assumptions, what are the justifications and so on. I missed that a little bit on that.

The study again is you have the 40 doses per two hours with the toddler and then we have this .15

milligram, which are divided by 40 which gives you .003.

And this is below the detection limit. That's the big problem here. And then we get this contribution to the brain.

And then we get this linear log log relationship. I already talked. Dave will comment with that also. And then we do this -- we need the half life stuff and then we do this back forward calculation, which gives this plateau curve.

This is what we are actually asked here. That is what I just wanted to reiterate again. So the question is how reasonable this is and how sure we can actually be when we have done that.

I think we have already touched a little bit in the morning the question of sensitivity analysis. Is this one scenario really sufficient to cover the whole problem would be a question.

Yes. I would stop at the moment for this part. And then we go actually from this calculation, you know, we got this seven -- this MOE of 70 and this MOE of 70 was divided by four, then we get more or less the 20.

Then this 20 was used for this biomonitoring study, which I -- we get some information by the document, but not very much information.

So I'm not very convinced about the design of this biomonitoring study where people had been just given the compound and they could use it and then they monitored it by the urine over one day and up to four days.

The question is how have these people actually behaved. I think if you do -- I do such a field study, I have to really record how people -- what people do over these days exactly in order to get some more information like you do for instance in an occupational study where you have the job exposure measures and all these things going on.

I think that would be a question I would have on that study.

The other thing is, of course, if you go this step further, that's good, I think, that we put both questions together now, you get even more -- the uncertainty even build up finally into this magic number of 20.

And the question is really how valid or how variable is actually what we get finally because then this number is used in order to get back to some concentration values.

DR. HEERINGA: Thank you, Dr. Edler. Dr. Hattis is the next discussant.

DR. HATTIS: I think I'm going to put on another couple slides. I want to comment. One of the elements of the projection is, in fact, a log log interpolation. Basically, log brain concentration versus log external dose.

And the main point that I have with that is that that doesn't -- it is very frequently used empirically as was done in this case.

But it doesn't have a strong mechanistic foundation. There is no theoretical mechanism that gives you that kind of relationships.

The best -- I believe it will be better to use an assumption of a saturation of a Michaelis Menten detoxification process probably in the liver that's a more appropriate model to model any nonlinearity.

This was, in fact, done by Woody Setzer for the cumulative dose exposure study for the organophosphates. So I would recommend since he has already got that algorithm -- well, applying that algorithm or some, you know, close derivative of it to this case.

I think that would allow you to take into account both the modest amount of non linearity in the relationship that was observed -- and I can show it on that slide if we can get it on there.

DR. HEERINGA: While Dale is getting that ready, for the benefit of the audience, Woody Setzer is with the Environmental Protection Agency, Office of Research.

DR. HATTIS: Right. And he is a wonderful biostatistician.

DR. PERFETTI: I will tell him you said that, Dr. Hattis.

DR. HATTIS: Yes, he is.

DR. PERFETTI: We all know that. Except he is not here to appreciate it.

DR. HATTIS: Anyhow, so can I get my first two slides.

This is the log log plot. Unfortunately -- and this is a good fit. This is not a bad -- this is not unreasonable.

But theoretically, you should be getting to a straight linear relationship at the limit of low doses.

Because once you get down below the level where there is an appreciable saturation, the Michaelis Menten kinetics essentially translates into a linear dose response.

So the slope of that, even though that fits well, the slope it has to change at some level. And I think that you have enough information to model that in the existing data -- and if you collected a bit more data.

That modeling should take into account ideally both the brain cholinesterase data -- brain carbaryl concentration data and the apparent change in the half life that you observe from the plasma levels as a function of dose.

I think between those two data sets you have plenty of information to make a better guess at the dose response. So I would tend to use that.

The next slide has a very crude linear plot. And I don't have error bars for the data points. You can make error bars for those data points.

It is not completely obvious that you can reject the linear model because we don't know the uncertainty of each of the points. It's unlikely that there is in fact some non linearity there at the high dose.

But in theory, that non linearity ought to disappear and it is a modeling question exactly where you think it does and what an appropriate confidence distribution for the low dose behavior ought to be.

As general comments, I think it should be a usual practice that all the presentations of data should have some measures of dispersion of some sort so that the analysts are aware of the extent of experimental error.

Now, in fact, some of the underlying documents that were provided to the panel have some -- at least provide the individual data points.

I could have, if I had enough time, I could have calculated that. It is partly my lack of time. But in any event, it would be helpful to the reviewers to have some

analysis.

And in fact, you are going to need that later when you do confidence distributions on all of these things for the overall analysis.

DR. HEERINGA: Additional comments?

DR. HATTIS: No.

DR. HEERINGA: Very good. At this point we will come back.

The next discussant would be Dr. MacDonald, Peter, if you have something to add at this point.

DR. MACDONALD: I'm going to rely on scientific intuition here. What I see is a model that is at once oversimplified and too detailed for a different species in a very different context put together with a lot of guesswork. I have no confidence that the result means anything.

DR. HEERINGA: That's to the point. Dr. Riviere, can you expand on that.

DR. RIVIERE: Yes, I can expand on that. I'm going to try focus on a couple points on just the use of that model, which essentially is the relationship of the

20 times per hour ingestion of carbaryl for two hours in humans, which, essentially, is a dose for every three minutes compared to what was done in the rat.

And the point of this is try to extrapolate an experimentally impossible thing to conduct by individual dosing into figure out what would the effect be.

Basically, the assumption on accumulation occurring, if you have a 15 minute half life, and I am going to talk about half life later on, but it falls into that discussion we just had, then your accumulation is going to occur, a plateau is going to be reached. And that's fine.

The approach is sound. It is used all the time in parental pharmacokinetics and multiple dose regimens. But I do have concerns when you are applying a three minute dose interval to an oral situation.

I have seen tons and tons of rat and other data, oral absorption data, and variability is astronomical.

I take the argument that since you saw such an early peak that there is absorption occurring fast from somewhere. That could be from the stomach. That could

also be just from a rapid gastric dumping into the intestines immediately from the initial dosing.

My concern with is repeated dosing every three minutes is not necessarily going to result in bolus absorption. The rat is very different than the human on that line.

And these kids are going to be outside. Food is a factor. Fluid is a factor. Heat stress is a factor in gastric emptying time.

Once we now take the human scenario in that line, I'm almost guaranteed you are going to either have modulation of that three minute dose and you are not going to have these nice little discrete three minute increases that it is going to be modulated by what is happening to the gastric emptying time. And that goes in both directions.

It is also a cholinergic drug which we have to remember increases gastrointestinal motility and spreads it where the potential absorption could occur.

I think the approach is sound from the point of thinking you can break that dose up and you can get to

what the accumulated area is.

But applied to such a variable route as GI dosing is, you know, the assumptions really need to be investigated.

The other end of that is I have concern with what the actual half life used in those calculations is.

On the brain cholinesterase, half life of carbaryl in the brain is important. But that's not the thing determining overall carbaryl disposition in the body.

And those half lives are more variable. In that line, the second thing is just taking that first half life and calling that the half life.

That half life, it is a multi exponential process. That first half life encompasses the elimination and distribution.

And so, again, I would suggest instead of just looking at a dropped in half in 15 minutes to actually fit that to some kind of a model and get some idea of what that number really should be.

Again, this all assumes linearity. As we

discussed, I'm not sure what three points. You can actually pick out the difference of log log versus a linear model.

The key is you don't know if it is linear or not. There is no uncertainty built into that calculation.

What you just did, which is amply shown previously on the accumulation, is very dependent upon linear kinetics. If they are not, then that could be different.

DR. HEERINGA: Thank you, Dr. Riviera. Dr. Brimijoin.

DR. BRIMIJOIN: I have only got one thing. It is more maybe in the nature of a question for possibly further comment from my more learned pharmacokinetic modeling colleagues.

But so I'm just -- one key part of this last part of this Question 2 specifically deals with the issue of the margin of exposure.

And I guess the conventional way to do margin of exposure is to find what is the no effect level and divide that by the actual expected exposure.

But so what we're -- Bayer has come up with a different approach to this, and the approach results in a much larger and supposedly more reassuring MOE.

As a fairly naive person about such things, I can't help asking myself if this occurs, how much of this increase, five fold increase in the MOE is coming from what I see as an inappropriate focus on the half life of the compound in the brain as opposed to the half life of the compound's effect in the brain.

So just instinctively and intuitively, I feel that that must account for it. And I will go on record as sticking my neck out not having done the necessary calculations and computations and saying that I have that feeling.

And therefore, I mistrust the new MOE, although it is based theoretically on a much more sophisticated approach to the estimation of such things.

And if other panel members can explain why that's wrong, then I'll be very happy. If they agree, then I think this is something that will have to go into the comment.

DR. HEERINGA: Thank you very much. I'm sure we will have comment on that. Dr. Lu.

DR. LU: Just a quick couple points here.

The study design for the mixed dose model is flawed. Because if all we believe the half life recovery is so short, then you wait another hour to give another oral dose, the previous oral dose becomes insignificant to the whole picture of pharmacokinetic analysis. That's something I want to point out.

To overcome this flaw is to kind of echo one of the panel. I think Dr. Wheeler says that there is a possibility you can do a gavage calculation using micro feeding tube connected to a time controlled perfusion pump.

That way you don't have to go -- I think animal committee member will be okay with this type of a study protocol. I don't think we have to spend more human power on this.

The other thing is how you want to -- just give me a second.

The other flaw associated with this mixed dose

study, if you look at Table 4, that's the document provided by EPA on page 13, half life for carbaryl varied according to the dose administered through the same route of administration.

I think the fundamental pharmacokinetics is the half life stayed the same regardless if you gave 1 milligram per kilogram or 100 milligram per kilogram dose to the same route, to the -- to the rat through the same route.

So the half life -- actually, some of the half life varied by 100 percent. And half life is the heart and sole of the whole report that was made today.

So if the half life already have some problem, then the outcome of this whole thing is just problematic. So that's why I kind of stressed the importance of performing the whole spectrum of pharmacokinetics analysis using modeling. If your data is good, the data including concentration, the time is good, the model will give you somewhat close half life. But not the half life present on Table 4.

DR. HEERINGA: Thank you, Dr. Lu. Dr. Kehrer.

DR. KEHRER: No.

DR. HEERINGA: No additional comments to add at this point. I think, Dr. Hattis, you had comments you wanted to add.

DR. HATTIS: Yes. I haven't done the -- this is in response to Dr. Brimijoin's comment. I haven't done the revised MOE calculation myself.

But I think Dr. Brimijoin's instinct is correct that because the longer half life of the cholinesterase inhibition will mean that the different doses will interact more and their effects will accumulate more.

It indicates to me that the MOE calculation will lead to a smaller MOE than the one based on the -- maybe not all the way as small as EPA's original calculation of a -- that is straight based on total daily dose.

So that's my guess about that.

DR. HEERINGA: Dr. Portier.

DR. PORTIER: As I read through this report and thought about these two questions, it strikes me that in a sense what we're talking about here is that an exposure scenario has kind of been tacked on to the back of the PK

model.

And this opens up the whole model to criticism of oversimplification as Peter MacDonald kind of said it. I guess the approach that I was expecting to see, and maybe others expect to see, are the kind of stuff we're going to talk about in the meeting tomorrow, the December 3 meeting, where we have an exposure scenario model that is kind of separated from a PBPKPD model.

And we concentrate on getting the exposure scenario to look right and then get the model in enough detail that we feel comfortable with it and then we try to put them together.

As I look at this, I feel like we have got too simple a pharmacokinetic model and too simple an exposure model and we have tried to put them together and it just doesn't seem to work.

When you think about the multi route study that we just looked at in question one in this light, the design of the multi route study should have been to look at interactions in the dynamics and see whether those two routes, two possible dosings cause an interaction.

That's the reason you do two factors in an experiment, is to look for interaction. But the purpose seemed to be more to mimic an exposure.

I get confused on those kinds of things. Maybe I will open it up to the panel as to whether they see kind of a similar view.

DR. HEERINGA: Dr. Fischer.

DR. FISCHER: Well, I agree with Dr. Portier anyway. I think he is right that the multi dose experiment, not multi dose, but the multi route of dosing experiment, really, I looked at it as a look for interactions, possibly.

Because I don't think, as I said before, that the experiment mimicked the kind of dosing that goes on. And because it doesn't, we have to go through all these calculations to try to make things fit.

It just doesn't seem to fit. So I think we're doing probably the wrong thing here.

I think there was a suggestion made earlier to use two separate sets of data, one from dermal exposure and the other from oral exposure. And do the modeling

necessary with each of those, if you want to know what is going to happen or have an idea of what is going to happen when you mix the two routes of administration.

DR. HEERINGA: Dr. Edler.

DR. EDLER: Actually, I agree with all this criticism we have with this study. I really want that we don't forget actually that we need an assessment of the variations we have.

And we need a real statistical analysis of all this data and even go further doing some reasonable uncertainty analysis, what is going on.

My question is still where the whole study started. Namely, that they are in some way in a range of exposure in these toddlers where they cannot measure much.

So they will have this problem to do some extrapolations going down. When I saw that, and it was really hard to read that whole thing, that's another issue, when I saw that -- it has to be said, I think.

I thought, well, what can they do. But then I see only one scenario. I see what has been built up and where we have these curves and I thought this couldn't be

the only thing what is going on.

I would imagine different scenarios. Now we hear a lot of other things. We hear there is nutrition in there perhaps. Things could be in the stomach which will disturb the pharmacokinetics.

This really confirms to me more that we have more scenarios going on. So I think that there could be a big simulation study behind that.

DR. HEERINGA: I think at this point we have had a fair amount of discussion about what I would call part B. I think there is a key component in part C.

Maybe Peter has addressed that most directly. I think we need to help here and think through this issue of we have done work, even if we could did work in the rats with regard to dosing and measurement, how, then, do we make the leap to kinetics in the human, excuse me, the exposure levels, margin of exposure levels in human.

Specifically, I'm referring to the last part of part C, please comment on whether this approach is appropriate for extrapolating from results in the rat pharmacokinetic study to do the biomonitoring study.

In other words, when we actually use this MOE ratio, to make the jump from the rat to the human child.

Specific comments on that. Dr. Reed.

DR. REED: Not about this. I was just going to add a comment to what we're talking about in the mixture setting.

What I have in mind is that, okay, so you have the mixed dosing study. But you also have the kinetic separate routes from the first study, from the main study.

And I was hoping that someone could take a look at, sort of, modeling the situation of a mixed route study and see how close you can come to with the single route information that you have from the first study.

That was my sort of comment to that. It might not come out very close at all to each other. But at least we could identify what might be the factor that would make them not the same.

DR. HEERINGA: Let's go back to Dr. Hattis.

DR. HATTIS: Not to be a broken record, but a modeling approach provides the most, I think, natural context to take into account the small number of pieces of

information we have about the people relative to the rats.

And so if we know something different about human dermal absorption relative to rats, and I think that Dr. Bunge has researched that extensively, then we should put that into the mix of analysis.

In the document there is quotations of some at least slightly different regeneration rates for the rat. Acetyl cholinesterase versus the human.

It would be natural to put that in the MOE determination as well, it seems to me. I don't know if we know anything at all about inhibition of brain cholinesterase from observed levels in people.

But if we knew something about the ratio of red cell cholinesterase inhibition per unit dose at high doses, then it seems to me that would be a natural part of the edition as well as at least relying on fairly well established scaling factors and uncertainties in those for the enzymatic reactions for the detoxification.

DR. HEERINGA: Dr. MacDonald.

DR. MACDONALD: I think in particular we need a

more realistic model of the different routes in which the chemical can be picked up by children making contact with the lawn.

There are so many other ways than hand to mouth. Some of these have been suggested already. Accumulating on toys, accumulating on pets getting into the house and then having more contact later.

I think it has really been too oversimplified. And the rat studies are just too different the way they -- with bolus and dermal exposure of the rats. It is just too different from the child behavior that we know happens.

DR. HEERINGA: I'm looking to the panel for additional -- yes. Dr. Kehrer.

DR. KEHRER: You actually asked something more specific here a minute ago about that adjustment factor of 20 that they used.

I actually have some concerns about that. By taking a previous model, which has its own flaws that we haven't discussed at all, and using an adjustment factor for a new model to make it closer to the previous model,

I have some problems with that.

I would think each model should stand pretty much on their own open. And if there are reasons why the two numbers don't match, then you should be looking within the model to see why that's the case rather than throwing in an adjustment factor.

DR. HEERINGA: Dr. Riviere, did you have a comment?

DR. RIVIERE: No.

DR. HEERINGA: Dr. Pessah.

DR. PESSAH: I just had one more question getting back to cholinesterase as an endpoint given how rapidly this stuff regenerates.

Dr. Chambers might talk about this. Practicality in the lab when you get to sample 30 minutes nominally to work up to samples for measurement, another 30 minutes to make measurement or set of measurements, what reliability do you have even in ballpark that you have actually measured the actual level of inhibition.

DR. CHAMBERS: I haven't worked with carbamates. I thought they recover even faster than the

dimethyl organophosphates. We certainly struggle with the dimethyl organophosphates.

We don't grind it and assay it immediately. It recovers before your eyes, basically. I think these measurements with carbamates are probably somewhat off too.

DR. HEERINGA: Dr. Lowit.

DR. LOWIT: Just to get at sort of your question and Dr. Chambers' response.

When some subset of this group comes back to talk to all of you again in February about the carbamate cumulative assessment, one of the issues we'll talk about will be the one you just brought up. But sort of a quick and dirty.

From what we can tell with radio metric data versus the typical element, predominantly most of the registrants, including Bayer, are very aware of this issue and tend to take extreme precautions.

And we'll show the data later. We feel pretty good about the cholinesterase data. If you assume the radio metric is sort of the gold standard, the way that

the contract labs do their experiments, it is pretty reasonable.

DR. HEERINGA: You mentioned this data would be shown in later sessions.

DR. LOWIT: Not until February.

DR. HEERINGA: That is what I assumed you meant. Thank you very much, Dr. Lowit.

At this point in time, I would like to turn to the EPA to see if the panel has addressed each of these three points.

DR. FARWELL: Let me check. We're good.

DR. HEERINGA: It is 3 o'clock. I would like to take a 10 minute break give people a chance to relax a little bit and then come back for concluding comments from the panel.

We indicated that panelists would have an opportunity to review their comments and make additional comments scientifically appropriate to this topic.

Let's reconvene here at 3:15 to conclude today's session. Thank you very much.

(Thereupon, a brief recess was taken.)

DR. HEERINGA: Welcome back to the conclusion of today's session of the FIFRA Scientific Advisory Panel. We had just concluded our discussion of charge question number 2.

But before we move on to general comments and a wrap-up, I would like to offer both the panel or the members of the EPA, staff of the EPA, if you have additional questions that you would like to pose, I guess for the EPA, whether there are clarifications that came to mind you would like to seek with panel members, or panel members, whether there is anything you would like to mention to include that you think might be incorporated in the report.

Dr. Hattis.

DR. HATTIS: I want to mention that I'm doing a revised set of graphs based on the 1.7 hour half life so that those will be reflected in what we put in our comments.

DR. HEERINGA: Thank you, Dale. At this point, I guess, what I would like to do is to turn to the members of the panel.

I will systematically round the panel to see if there are any general comments pertinent to the scientific topic of the pharmacokinetic modeling.

At this point maybe I could begin with Dr. Harry.

DR. HARRY: Well, since it is a bit outside my expertise, but listening to the comments around the table from the panel members as well as what EPA has presented and Bayer has presented, I do think it is -- you should be applauded for taking this step and then starting to get feedback of maybe how to refine it to make it applicable.

And I do think we do need to remember why it was done in the first place while we're making comments. And not to try to get more out of this study than what you had planned on it presenting to you when you initiated it -- just when we're making our deliberations.

DR. HEERINGA: Dr. Wheeler?

Dr. Bunge had to leave to catch her late afternoon flight back to Colorado.

Dr. Stinchcomb.

DR. STINCHCOMB: I would like to say that that

was -- it is a very good start.

And I just -- for the skin area, I think it is going to be important for future work to always compare human skin diffusion with your animal of interest, which seems to be the rat in toxicology, just to compare the skin permeation.

Because sometimes there is always a 10 fold difference and sometimes there is no difference. And sometimes it goes the other way. So that should always be incorporated, I would think, in every model.

DR. HEERINGA: Dr. Pessah? Dr. Fischer, any additional? Dr. Reed?

Let me go over to Dr. MacDonald.

DR. MACDONALD: No comment.

DR. HEERINGA: Dr. Riviere? Dr. Brimijoin? Dr. Lu.

DR. LU: Just a quick comment. That very little result will present from the human, the lawn treatment study, the urinary, 1-naphthol study. I think that Bayer should have lots of data to work on.

I think that would be a very interesting topic

as well.

With such a rapid metabolism of carbaryl in the (inaudible) anyway, I almost believe that urine will be your best choice for modeling the exposure and the risk, not the peak concentration point.

I would like to see more work on the urinary data.

DR. HEERINGA: Dr. Kehrer.

DR. KEHRER: I also commend them for the study and I also think carbaryl is a really good compound to choose to be trying to implement some of the pharmacokinetic data to establish risk limits.

I think the data they have has some limitations as has been pointed out. But the general validity of the approach seems quite clear.

I think it is as good or maybe even slightly better than the current procedures that have been used to establish exposure limits for carbaryl.

I hope that with some better peak level data and the consideration of kinetic effects in cholinesterase, that this can be proceeded with.

DR. HEERINGA: Thank you very much.

Dr Hattis.

DR. HATTIS: I want to say some of the comments that I have made and some of the folks have made are necessarily critical.

But that this should be understood not as a wasted effort, but as a weigh station along the -- as part of the advance of our technical understanding.

And that even though it can be discouraging not to get the answer completely right the first time or the seventh -- understand what we see today might not be the first draft.

You know, that this is, in fact, a way of -- the way, in fact, that science has to proceed by critically reevaluating and putting the same pieces together in a different way.

DR. HEERINGA: Dr. Edler.

DR. EDLER: I think it is a difficult task, actually, which had been started with this study and started right into the whole area, where data come in and the modeling comes in so on.

When we do that, actually, we have three levels. We have the exposure modeling, we have the PK kinetic modeling, have the PD, the dynamic modeling.

I think we really have to separate that out in the whole outline. Otherwise, we get -- always have a hard work not to get confused by that.

DR. HEERINGA: Thank you. Dr. Handwerger.

DR. HANDWERGER: As a pediatrician, I anxiously await a mathematical model of toddler behavior.

DR. HEERINGA: You don't have it, Ken. Dr. Chambers.

DR. CHAMBERS: I'll reiterate what I said earlier. I really think conceptually this is a very good starting approach for compounds that have a short half life, metabolize readily and have a quick action.

DR. HEERINGA: Dr. Isom?

DR. HEERINGA: At this point, I guess having heard final comments from the members of the panel, I will turn to the EPA staff and presenters to see if you have any additional questions or comments that you would like.

MR. DAWSON: I think I'm the first one. I would

like to first of all thank the panel for your work in this area.

We view this as a very exciting time for us because we view it as a first step and kind of next generation of risk analysis. We appreciate your thoughts.

Also, I think to kind of reflect a lot of the panel's comments and just to let you know where we are with this, we have this information that was considered today, but we're also very actively pursuing exactly what you all have been discussing a lot today as far as additional use of these data through some modeling efforts that Dr. Farwell also touched on earlier with -- are also research and development.

And I know Bayer as well is pursuing additional modeling efforts with these data and potentially more data. So we're very actively working in this area, just to let you know where we are.

Thank you very much.

DR. HEERINGA: Dr. Perfetti.

DR. PERFETTI: I would like to thank the panel again for all your comments and suggestions. It was very

helpful.

I would like to echo Jeff's comment that this is an ongoing effort. And as you all realize, all of you who have been with us all these years during the OP cumulative we didn't get it right the first time or the second time or the seventh time. But after 26 reviews with the panels, we finally got it right.

Again, I would just like to make sure everybody, especially the public, realizes this is an ongoing effort and this is only the first step.

DR. HEERINGA: At this point I would like to echo the comments of the panel, too. Again, this is a first step. It is a first step in a process, in a direction that a number of the SAP meetings have called for over the last three or four or five years that I have been involved in various capacities.

And I think we recognize it as a first step. And while there have been some criticisms of certain aspects of this, I think the process is viewed as a direction forward.

And we expect continued refinement and continued

review of this process over the coming years. So again, my thanks to all of the expert panelists who were here to contribute, to the staff of the EPA, to the staff of Bayer CropSciences and also to our public commenters for their contributions to this meeting.

Before I close, I would like to turn back to our designated federal official, Joe Bailey, to see if you have additional remarks.

Mr. BAILEY: Just on behalf of the Office of Science Coordination and Policy, I want to thank the panel for all of the time they have taken to prepare for the meeting and for being here today.

And thank the EPA Office of Pesticide Programs for their presentation, Bayer's clarification of points of interest.

And also thank our small group, but resilient group of members of the public who have been here today. Thank you.

DR. HEERINGA: Again, the deliberations here, the comments will appear in the form of a report from the SAP to the EPA.

That report will constitute minutes of this meeting. It will be organized and include the material that has been discussed today. I think that first drafts will be prepared.

The report is expected to be available six to eight weeks. And we'll push as hard as we can to make it on the shorter end of that spectrum.

If there are no additional questions or comments today, I would like to call this meeting of the FIFRA SAP to a close, again, thanking everybody for their participation.

I suspect we will see some of you back here tomorrow morning for continuation on the cumulative risk assessment.

Thank you very much, everybody.

(Whereupon, the meeting concluded at 3:40 p.m.)

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I, Frances M. Freeman, Stenotype Reporter, do hereby certify that the foregoing proceedings were reported by me in stenotypy, transcribed under my direction and are a verbatim record of the proceedings had.

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